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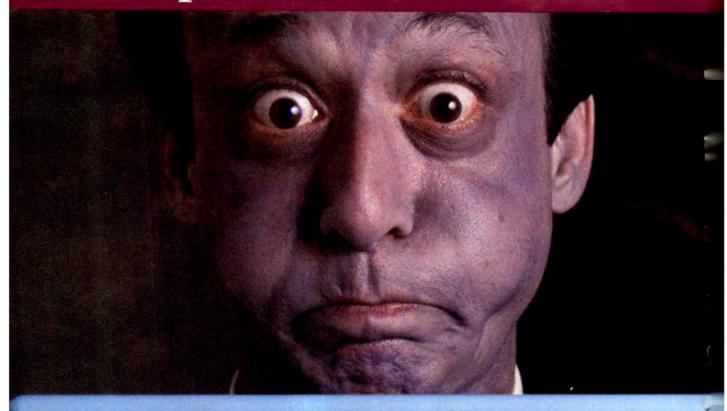
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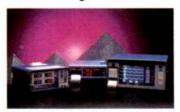
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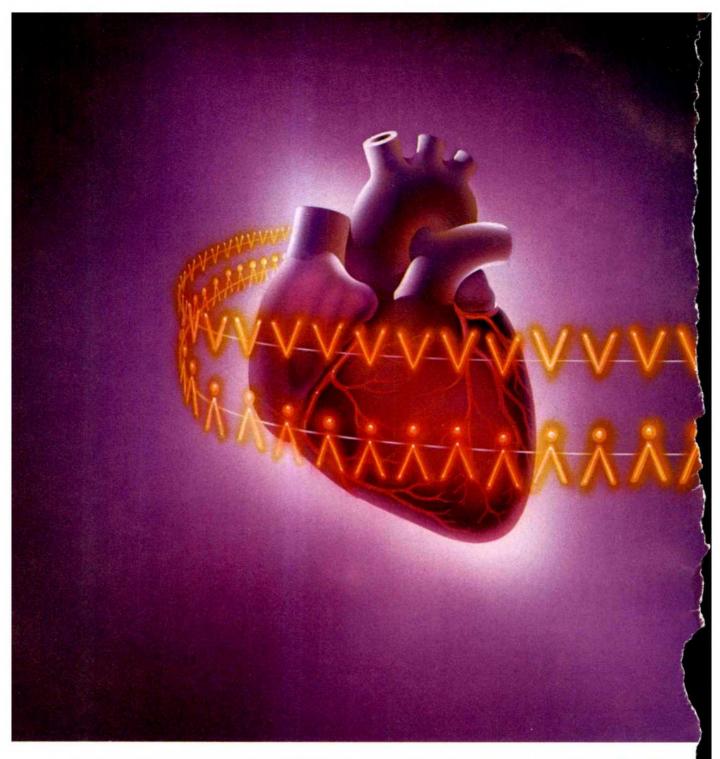
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CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with lentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by. 1) administration of up to $\frac{1}{4}$ of the full paralyzing dose of a non-depclarizing neuromuscular blocking agent just prior to-aliministration of SUFENTA at dosages of up to $8\,\mu\text{g/kg}$, 2) administration of a full paralyzing dose of a neuromuscular blocking agent

following loss of consciousness when SUFENTA is used in anesthetic dosages (above $\theta \mu g/kg$) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuro-muscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above $\theta \mu g/kg$) The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debili tated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital, signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid analgenists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid analgenist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesis is accompanied by respiratory depression and diminished sensitivity to CO₂. Stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decrease respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENI should be administered with caution due to the importance of these organs in the metabolism and excretion

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*regnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when iven in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were set probably due to maternal toxicity (decreased food consumption with increased mortality) following olonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. UFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

.abor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous 1.0_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anxia, which preclude any meaningful interpretation of the restance.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) in bradycarda (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia Gastrointestinal: nauseo, vomiting Respiratory: apnea, postoperative respiratory depression, bronchospasm Dermatological: itching, erythema Central Nervous System: chills

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSABE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LO₂₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LO₂₅₀ in other species). Intravenous administration of an opioid antagonist such as naioxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or agnea. A patent airway must be mainfained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).



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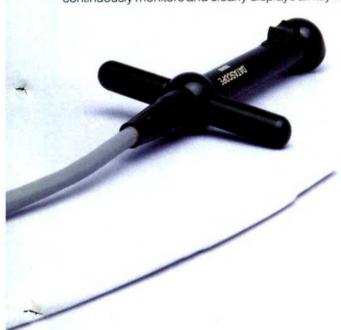
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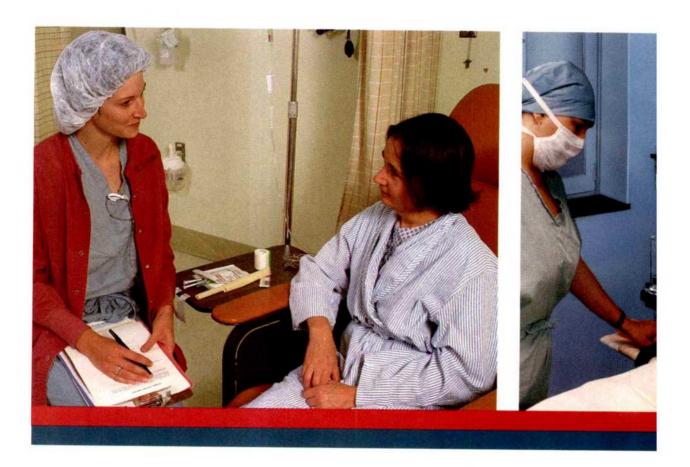
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2€ ± 4	1.20	0.66
44 ± 7	1.15	0.50

Induction of and recovery from isofluence enesthesis are supid. Isoflurane has a mild pumpency which limits the rate of induction, although excessive saletwine or ranchostronochial secretions do not expert to be stimulated. Pharyngeal and saryngeal reflexes are readily obtunded. The level of anothesis may be changed rapidly with soflurane are profound respiratory degreesant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anosthesis may be changed rapidly with increased, tital volume doensees and respiratory rate is unchanged. This depression is partially reversed by songical simulation, even at deeper levels of anothesis. Isoflurane seeded a figh seponder reminiscent of that seed with debug there and enflurance seeded a figh seponder reminiscent of that seed with debug there are deflurance. Blood pressure are researched to that seed with debug there are deflurance and the seeded of the see

INDICATIONS AND USAGE

FORANK (sochmans, USF) may be used for induction and maintenance of general ansethesis. Adequate data have not been developed to establish its application in obstatrical assethesis.

CONTRAINDICATIONS

Known sensitivity to FORANK (seofturans, USP) or to other halogenated agenta. Known or suspected genetic susceptibility to malignant hyperthermia.

Since levels of enesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression recommends a respiratory depression

potients undergoing abortions.

FORARE declarance, USEP marketly increases carebral blood flow at deeper levels of anesthesis. These may be a transient rise in corebral spinal fluid pressure which is fully reveable with hyperventilation.

PRECAUTIONS

PRECIAUTIONS

General: As with any potent general ansethetic, FORANE (softmans, UEP) should only be administered in an adequately equipped mesthetining environment by those who see lemilies with the planmacology of the drug and qualitative principal manages the ansethetized patient. Information to Patiesses is estimated, as well as other general ansethetics, mey cause a slight document in instinctual function for 2 or 3 days following unerthesis. As with other sessethetics, anall changes in moods and symptoms may persist for up to 6 days after

observed.

Dreg Interactions: Isoflurane potentiates the muscle relevant effect of all muscle relevants, most notably nondepolarizing muscle relevants, and MAC (minimum alwoolar concentration) is retivosed by concomitant administration of N₂O.

See CLINICAL PHARMACOLOGY.

Carrinogenesis: Swiss ICR mine were given neoflurane to determine whether such exposure might induce neoplasts. Isoflusne was given at 12, 18 and 162 MAC for four in-tiero exposures and for 24 exposures to the pupe during the first nine weeks of the number of the control of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine weeks of the number of the pupe during the first nine when the number of the

during programcy only it the posteriors remote partners are produced that the form of the Russiag Mothesis: It is not known whether this droug is exerted in human milk. Because many drugs are extrated in human milk, caution should be examined when isoflurance is administrated to a numbing woman.

Malignant Hyperthermia: In succeptible individuals, isoflurance ensethesis may trigone a elected monethy-permote produced syndrome known as malignant hyperthermia. The syndrome includes nonspecific status such as muscle rigidity, techycamils, techypnea, cyanosis, arrhythmias, retrythmias, structurals, the succeptible structure of the second many produced and unstable blood pressure. (It should also be noted that many of these nonspecific stymesy proper with light nesetheses, acute proposis, etc.) An increase in ownell metabolism may be reducted in the feether of the proposis, etc.) An increase in ownell metabolism and a necessate quality is not the first sign of sugmented metabolism and an increased used of the constitution of triggering signatic (e.g., nothurance), administration of intravenous charicolene sordium, and application of supportive therapy includes vigorous efforts to sestion body temperature to normal, respursory and carculatory support as indicated, and management of establyte-disch-lane demograments. (Consult presenting information for duntolene sordium intravenous for additional information on patient management.) Recal faiture may appear states, and urms flow should be sustained if possible.

ADVERSE REACTIONS

ADVERSE REACTIONS

Advance reactions economised in the administration of FORANE (softmains, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respitatory depression, hypotension and arrobutiniss. Silvering, nansea, womting and lieus have been observed in the postoperative period As with all other general ansethetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermus.

COURTDORAGE

Stop drug administration, establish a clear sirway and immate assisted or controlled ventilation with pure coppen.

DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION

Premedication: Parameterization should be selected according to the need of the individual
patient, taking imp account that secretions are weakly stimulated by FORANE
(sections). USF) and the beart rate tends to be increased. The use of anticholinerate
drugs is a matter of choice.

In space of the property of the property

tains no stabilizer. Nothing in the agent alters calibration or or

Incidurane contains no stabelizer. Nothing in the second stable supportions. Infraections induction with isoflurane in coxygen or in combination with oxygen-nitrous mode mixtures may produce coughing, breath holding, or laryagospasan. These lift-inuities may be svoked by the use of a hypnotic dose of an ultra-short-ecting sa-biturate inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical sin-ethesis in 7 to 10 minutes.

se-ethesis in 7 to 10 minutes. Emphysical levels of anesthesis may be sustained with a 1.0 to 2.6% ox-extraction when introduced is used concomitantly. An additional 0.5 to 1.0% may be southed when inchross cride is used concomitantly. An additional 0.5 to 1.0% may be southed when isolamns is given using oxygen alone. If added relevation is sequired, supplemental doses of muscle relaxants may be used. The level of thood presence during maintenance is an inverse function of isolamned conventuation in the absence of other complicating publisms. Excessive decreases may be one to depth of anosthesis and in such instances may be corrected by lightening armschesia.

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TRACRIUM® INJECTION

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Brief Summary

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¹Miller R. Rupp S. Fisher D. et al: Clinical pharmacology of vecuronium and atracurium. Anesth

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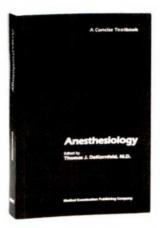
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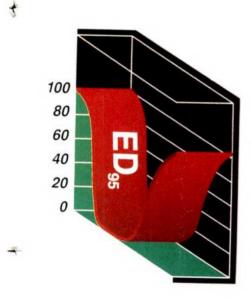


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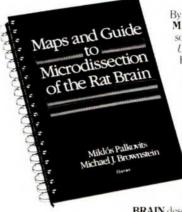
¹Hughes R: Atracurium: An Overview. *Br J Anaesth* 1986;58:2s-4s.
²Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p 98.

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> MICHAEL J. BROWN-STEIN, M.D., PH.D., Chief, Laboratory of Cell Biology, National Institute

of Mental Health, Bethesda, Maryland

An exceptional tool for the laboratory. MAPS AND CLIDE TO MICRO-DISSECTION OF THE RAT

BRAIN describes techniques for the dissection, identification, and removal of brain nuclei.

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Telencephalon / Rhinencephalon / Cerebral Cortex / Basal Ganglia / Septum / Amygdala / Diencephalon / Thalamus / Epithalamus / Metathalamus / Subthalamus / Preoptic Region / Hypothalamus / Mamillary Body / Mesencephalon / Pons / Cerebellum / Medulla Oblongata / Spinal Cord

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MOMENT-TO-MOMENT CONTROL

RAPID ONSET OF ACTION

for prompt control of hemodynamic response to surgical stimulation*

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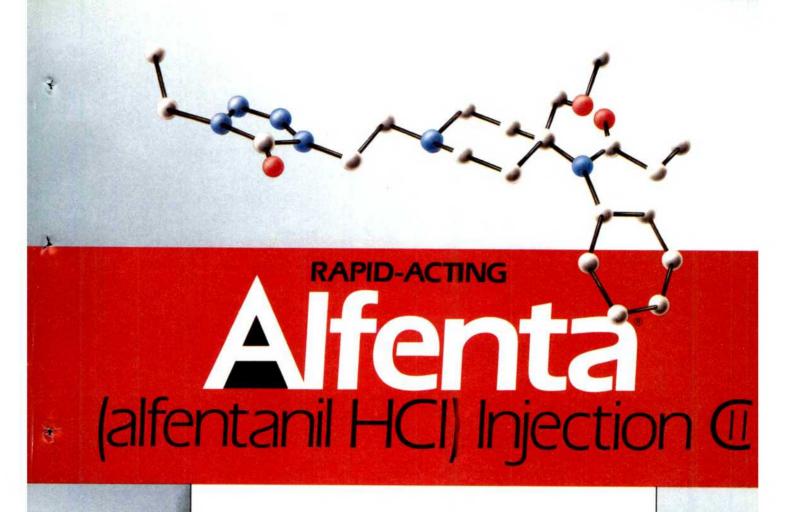
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CONTINUOUS INFUSION

for procedures lasting more than 45 minutes in intubated patients

*As with other opioids, hypotension and bradycardia have been reported.

'As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

P 24 566

See following page for brief summary of Prescribing Information.



AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

undergoing gynecologic surgery.

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing allentanil hydrochloride equivalent to 500 µg per mi of altentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIDIDS

AN OPIDID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND DXYGEN SHOULD BE READILY AVAILABLE BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT

MUST CONTINUE WELL AFTER SURGERY

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids.
ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of themsets and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to "V₀ of the full paralyzing dose of a neuromuscular blocking agent blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular studies. Adequate facilities should be available for nostoperative monitoring and verbilation of patients administered.

Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY

General: The initial dose of ALFENTA (altentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by aspearance of

delta waves in EEG, was 40% lower in geniatric patients than that needed in healthy young patients in patients with compromised liver function and in geniatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

may be reduced and postoperative recovery may be printinged.
Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to inductio Diazegam administered immediately prior to or in conjunction with high doses of ALFENTA-may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have

been successfully treated with atropine and conventional resuscitative methods

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or

ALFENTA influsion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA influsion should be discontinued at leas 10-15 minutes prior touthe end

of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid analgonists such as naioxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid analgonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ simulation which may persist into or recur in the postoperative period. Intraoperative hyperventiation may further after a sectionary after the contraction of postoperative response to CO₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiration. In such patients, opioids may addition decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA sho

administered with caution due to the importance of these organs in the metabolism and excretioned. A FER M should be **Drug Interactions:** Both the magnitude and duration of central nervous system and cardinvascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of onesor both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in dozes 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) (bllowing

prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rists or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported, therefore, use in labor and delivery is not recommended. **Nursing Mothers:** In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the follow ng table are derived from controlled and The reported unicidences of adverse reactions issted in the following table are derived from controlled and open clinical trials involving IRIS aptients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and heliothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of affentant induction, and by the type of surgery, e.g., hausea and vomiting have a higher incidence in patients

	ALFENTA (N — 785)	Fentanyl (N - 243)	Thiopental Sodium (N — 66)	Enflurane (N — 55)	Halethane (N — 18) %	Saline Placebo (N — 18) %
Gastrointestinal Nausea	28	44	14	5	n	22
Vamiting	18	31	11	5 9	13	22 17
Cardiovascular						
Bradycardia	14	7	8	0	0	0 11 0 0
Tachycardia	12	12 8 13 2	39	36	31 0 6	11
Hypotension	10	8	7	7	0	0
Hypertension	10 18 2	13	30 5	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0 2	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	D	0
CNS						
Dizziness	3 2	5 8	0 2	0	0	0
Sleepiness/ Postoperative Sedation				0		0 6
Rlurred Vision	2	2	n	n	0	n

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug sub-

stance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanii hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LOs₅₀ of ALFENTA is 43.050 g mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-619 mg/kg in guinnee pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific

logs. Intravenous administration of an opioid antagonist such as naioxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent arrway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to annage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alternanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Manufactured by Taylor Pharmacal Co. fo



Janssen Pharmaceutica Inc. Piscataway, NJ 08854

U.S. Patent No. 4.167.574 March 1987 49-7619901-M

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See preceding page for brief summary of Prescribing Information for ALFENTA® (alfentanil HCI) Injection ©

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY 62nd CONGRESS - March 5–9, 1988

Marriott-San Diego

(formerly Hotel Inter-Continental, San Diego, California)

PRELIMINARY MEETING INFORMATION

PROGRAM / REGISTRATION / HOTEL INFORMATION: Will be mailed mid-December to all IARS members. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland Office: 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephone: (216) 295-1124.

MEETING SCHEDULE: Registration: Saturday, March 5, 1-6 pm

Scientific Program: Sunday, March 6 through Wednesday, March 9

Exhibits: Sunday, March 6 through Tuesday, March 8

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture:
"Anesthesia, Science and Art"
Frank M. Standaert, MD, Dean of the Medical Faculty,
Medical College of Ohio at Toledo

REVIEW COURSE LECTURES:

J. Jeffrey Andrews, MD Jeffrey L. Apfelbaum, MD Paul G. Barash, MD Jonathan L. Benumof, MD D. Ryan Cook, MD Benjamin G. Covino, MD Judith H. Donegan, MD Edmond I. Eger II, MD John H. Eichhorn, MD Mieczysław Finster, MD Paul R. Hickey, MD John T. Martin, MD Charles H. McLeskey, MD Joseph M. Messick Jr, MD Ronald D. Miller, MD Richard L. McCammon, MD Terence M. Murphy, MB Walter S. Nimmo, MD Richard J. Palahniuk, MD J. Gerald Reves, MD Myer H. Rosenthal, MD John J. Savarese, MD Linda C. Stehling, MD John H. Tinker, MD Kevin K. Tremper, MD Paul F. White, MD

PANEL: New Perspectives in Pediatric Anesthesia Barbara W. Brandom, MD Lynn M. Broadman, MD D. Ryan Cook, MD

D. Ryan Cook, MD Paul R. Hickey, MD PANEL: Perioperative Blood Transfusion

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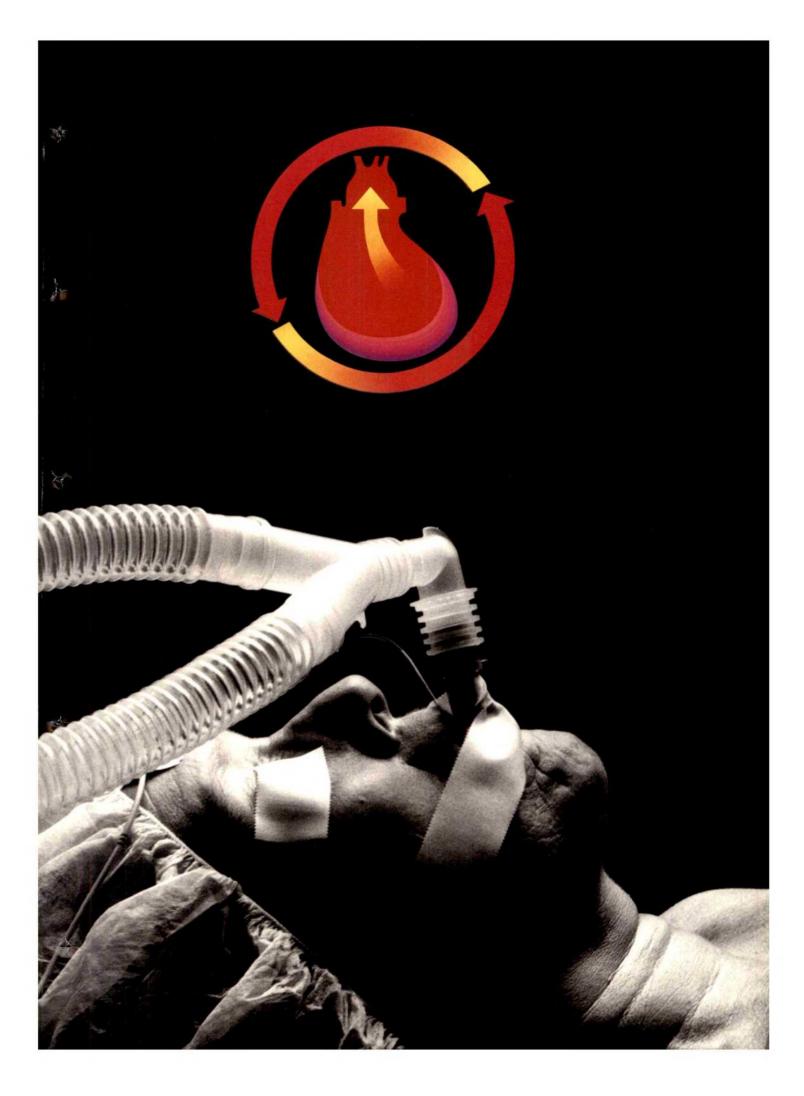
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CME CREDIT: ACCME/AMA: Category 1: 31 hours

SPECIAL AIR FARES: Both Delta Airlines and United Airlines, in cooperation with the IARS, will provide reduced fares for round-trip travel to San Diego. Full details will be included in the preliminary program mailing, or can be obtained by calling the following numbers and referring to IARS meeting and file/account numbers shown:

United: 1-800-521-4041—Account No. 8063-H; Delta: 1-800-241-6760—File No. P-0095

HOTELS: The headquarters hotel where all meetings and exhibits will be held is the Marriott-San Diego (formerly the Inter-Continental), 333 West Harbor Drive, San Diego, CA 92101. A limited number of rooms will also be available at the Omni Hotel. Reservations must be made on IARS meeting hotel reservation form.



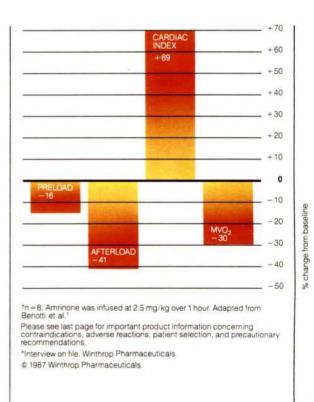
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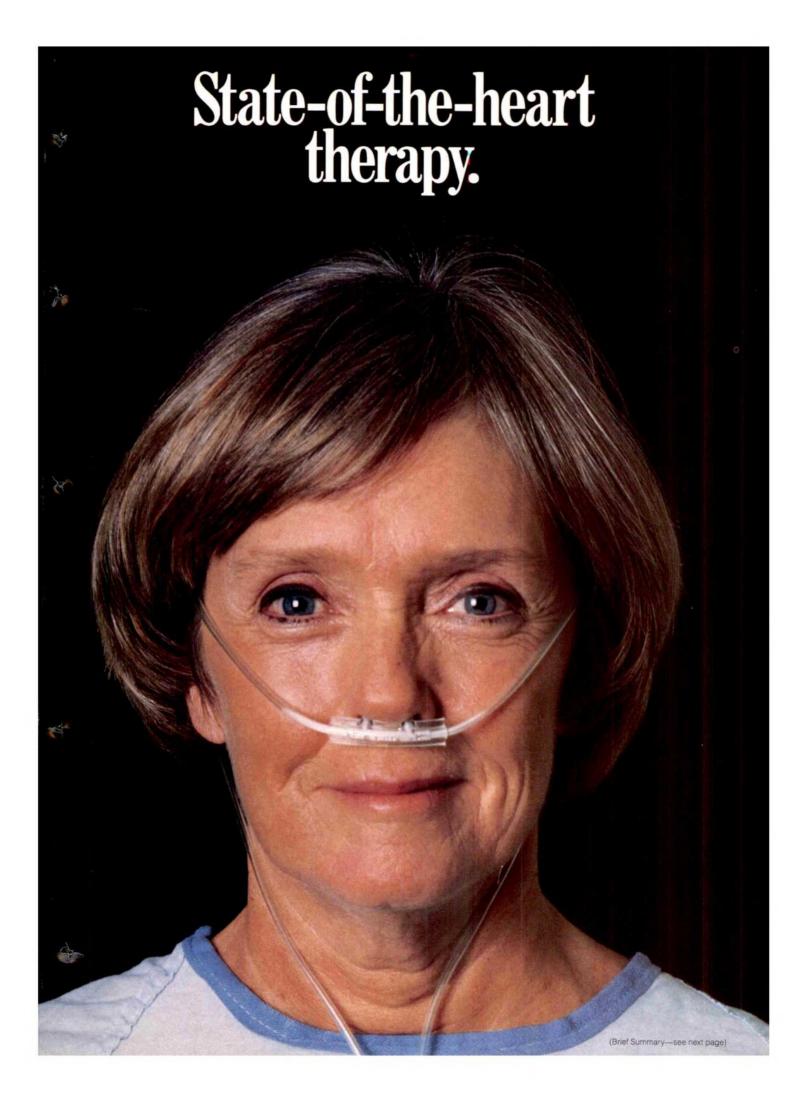


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- Unlike catecholamines, INOCOR does not act on the beta receptors may be effectively used in patients on beta blockers.
- INOCOR has not been shown to interact with anesthetic agents.

Please consult full product information before prescribing. A summary follows: INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

glycosides or catecholamines.

MOICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis,

closely monitored and who have not responded adequately to digitalis, duretics, and/or vasodilators.)

INDCO! lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INDCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied of longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsibilities.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients

who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to

PRECAUTIONS General: INOCOR lactate injection should not be used in

PRECAUTIONS General INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of influsion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS Fluid and electrolytes: Fluid and electrolyte changes and renal function should be carefully monitored during amminone lactate therapy improvement in cardiac output with resultant diuresis may necessite a reduction in the dose of diuretic. Potassium loss due to excessive diuresis. may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during

DRUG INTERACTIONS in a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate

injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol, hydralazine, prazosin, isosorbude dinitrate, nitroglycerine, chlorihalidone, ethacyriic acid, furosemide, hydrochiorothiazide, spiironolactone, captopril, heparin, warfarin, potassium supple-

ments, insulti, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with

Norpace® disappyramide should be undertaken with caution. **USE IN ACUITE MYOCARDIAL INFARCTION** INOCOR is not recommended.

for use in acute myocardial infarction. **USE IN CHILDREN**: Safety and effectiveness in children have not been

established USE IN PREDNANCY Pregnancy category C in New Zealand white rabbits, amminone has been shown to produce letal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral loses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amninone intravenously at the maximum dose used. 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amninone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in

ADVERSE FIEACTIONS Thrombocytopenia: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

patients.

Gastrointestimal effects. Gastrointestinal adverse reactions reported with NOCOR lactate injection during clinical use included nausea (17%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Gardiovascular effects. Cardiovascular adverse reactions reported with NOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%), Hepatic toxicity. In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, aminione shiwed dose-related hepatotoxicity manifested ether as enzyme elevation or hepatic cell necross or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of aminione. Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in gatients treated with oral aminione for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and asoftes (one case), myosins with interstitual shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first platent died, not recessarily of the possible reaction, while the last two resolved with discontinuation of the possible reaction, while the last two resolved with discontinuation of

therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS Platelet count reductions
Asymptomatic platelet count reduction (to less than 150,000/mm³) may be
reversed within one week of a decrease in drug dosage. Further, with no change
in drug dosage, the count may stabilize at lower than predrug levels without any
clinical sequelae. Predrug platelet counts and frequent platelet counts during
therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm3 occur, the following

actions may be considered:

• Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.

Decrease total daily dose.

Decordage load and oose.
 Discontinue amritione if, in the clinical judgment of the physician, risk exceeds
the potential benefit.
 Gastraintestinal side effects. While gastrointestinal side effects were seen
infrequently with IV therapy, should severe or debilitating ones occur, the
physician may wish to reduce dosage or discontinue the drug based on the
usual benefit to risk considerations.

issial benefit-to-risk considerations.
Hepatic toxicity: In clinical experience to date with IV administration, hepato toxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amritione therapy should be promptly discontinued.
If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amritioner and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.
HOW SUPPLIED Ampuls of 20 ml. sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0868-20). Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.

 Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. Circulation 1980:62:28-34



Dual-acting therapy, instead of catecholamines



Potentiation of Neuromuscular Blocking Agents by Calcium Channel Blockers in Rats

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BIKHAZI GB, LEUNG I, FLORES C, MIKATI HMJ, FOLDES FF. Potentiation of neuromuscular blocking agents by calcium channel blockers in rats. Anesth Analg 1988;67:1-8.

The effect of calcium channel blockers (Ca-antagonists) on the potency and reversibility of muscle relaxants (MR) was investigated in the in vitro phrenic nerve-hemidiaphragm and in vivo sciatic nerve-tibialis anterior preparation of rats. To increase the relevance of the experimental findings to the clinical situation, the [Ca++] and [Mg++] in vitro were the same as in the plasma of rats and humans and the stimulation parameters used in vitro and in vivo were similar to those that elicit voluntary movements of the muscles used. Both verapamil and nifedipine significantly decreased the I50 and I90 of d-tubocurarine (d-Tc), pancuronium, vecuronium, and atracurium in vitro and those of the first three MR in vivo (P < 0.001). In vitro, the depression of the force of contraction of the diaphragm (P)

caused by all the Ca-antagonist-MR combinations could be reversed only partially by washout, neostigmine, or 4aminopyridine. In vivo, because of limitations imposed by their cardiovascular depressant effect, the muscles were exposed to lower concentrations of Ca-antagonists for shorter periods. Under these circumstances the decrease of P caused by all Ca-antagonist-MR combinations recovered spontaneously close to control levels. This study indicates that acute administration of verapamil during anesthesia may increase MR potency, but it is unlikely that spontaneous recovery or reversibility of the residual neuromuscular (NM) block at the end of anesthesia will be significantly affected. However, long-term administration of Caantagonists may make difficult the reversal of the residual NM block.

Key Words: NEUROMUSCULAR RELAXANTS d-tubocurarine, pancuronium, vecuronium, atracurium. PHARMACOLOGY—calcium CHANNEL BLOCKERS, verapamil, nifedipine.

It has been reported that in relatively high concentrations, calcium channel blockers (Ca-antagonists) inhibit both the directly and indirectly elicited force of contraction (P) in in vitro nerve-muscle preparations of rats (1), frogs (2), and chicks (3). The depression of P caused by Ca-antagonists is only partially reversed by washout. Increasing the concentration of Ca⁺⁺ or adding 0.75 µM neostigmine or 40 µM 4-aminopyridine (4AP) to the organ baths has little or no antagonist effect (1). Some investigators found that in vivo, doses of Ca-antagonists that did not cause significant hypotension had little or no effect on P in rats (4), cats

(5), or rabbits (6). Others reported that in cats (7) 0.1-0.4 mg/kg verapamil decreased P significantly, more so during indirect than during direct stimulation, without any significant cardiovascular effect. Most investigators believe that Ca-channel blockers have both pre- and postsynaptic effects (3). It is conceivable that the relative importance of the preand postsynaptic component of the myoneural effect of Ca-antagonists varies in different species. (The term "myoneural" instead of neuromuscular (NM) is intended to signify that a compound not only affects NM transmission, it also modifies excitation-contraction coupling and/or muscular contractility.) The postsynaptic component appears to be most pronounced in rats (1), and greater in cats (7) than in dogs (8).

Whatever the site and mechanism of their neuromuscular (NM) effects, it was found by all investigators that Ca-antagonists increased the NM effect of muscle relaxants (MR) in both in vitro (2,3,9-12) and

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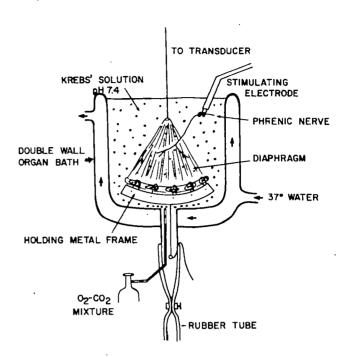
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in vivo (4-6,13) animal experiments. In most of the studies cited above, however, the interaction of a single Ca-antagonist, usually verapamil, with only a single MR has been investigated, and the combined effect of these compounds was not observed in both in vitro and in vivo nerve-muscle preparations of the same species. Furthermore, the extracellular [Ca⁺] of the bathing solutions used in the in vitro experiments was much higher than in human or animal plasmas (14) and, although in mammals voluntary muscle movements are elicited by short trains of tetani (15), low frequency single stimuli were employed both in vitro and in vivo. Extracellular [Ca⁻⁻] (14) and stimulation parameters (16) have great influence on the potency and reversibility of MR and other myoneurally active compounds. Therefore, it was decided to investigate the interaction of Caantagonists and MR using physiologic [Ca⁺⁺] (n vitro) and stimulation parameters (in vitro and in vivo). It was assumed that observation of the m70neural interaction of these two groups of compounds under these experimental conditions would be more relevant to the clinical situation than those employ∈d in earlier studies.

Anesthesiologists may have to deal with the interaction of Ca-antagonists and MR in patients who are on prolonged Ca-antagonist therapy before surgery or in others given one or two doses of verapamil IV for treatment of supraventricular paroxysmal tachycardia or reduction of ventricular rate associated with atrial fibrillation or flutter during anesthesia. In 33tients on Ca-antagonist maintenance therapy, these compounds may accumulate in the muscles. This accumulation is unlikely to occur in patients who receive verapamil IV during anesthesia. To simulate both situations we observed the interaction of the two most widely used Ca-antagonists and four MR in v.vo and three MR in vitro. Atracurium was only investigated in vitro. In vitro exposure to Ca-antagonists was relatively long and, similar to the situation in patients on maintenance therapy, these compounds could accumulate in the muscle. In vivo, becaus∈ ⊃f their cardiovascular depressant effect, only a single dose of Ca-antagonist could be used, and therefore there was no opportunity for their accumulation in muscle.

Methods

Male Sprague-Dawley rats of 300 to 400 g body weight were used in both the in vitro and in vivo experiments. For in vitro studies the rats were lightly



<u>Figure 1</u>. Schematic representation of the in vitro experimental setup.

anesthetized with ethyl ether and decapitated. The phrenic nerves and hemidiaphragms were dissected and suspended in organ baths (Fig. 1) in modified Krebs' solution (14) containing 1.4 mM CaCl₂ and 0.9 mM MgSO₄. In the presence of these [CaCl₂] and [MgSO₄], the physiologically important [Ca⁺⁺] (1.1 mM) and $[Mg^{++}]$ (0.8 mM) are the same as in human or rat plasma. The bath was aerated with 95% O_2 -5% CO₂ and its temperature was maintained at 37°C. The pH of the bath was between 7.38 and 7.42. The phrenic nerve was placed across bipolar platinum electrodes immersed in the organ bath and the hemidiaphragm was stimulated (Grass model S48B stimulator) indirectly with 0.1-second trains of 50 Hz, supramaximal, square wave impulses of 0.2 msecond duration every 20 seconds. Fifty-Hz stimulus frequency was selected because voluntary muscle movements in mammals are elicited with stimulation frequencies that correspond to the fusion frequency of the respective muscle (15). This was found to be 45-50 Hz for the diaphragm of rats (16). Before the start of stimulation, the optimal resting tension (10-15 g) was applied to the diaphragm. The isometric force of contraction (P) was quantitated with FT03 transducers and continuously recorded (Grass model 70 polygraph). After P became stable the cumulative dose response of d-Tc, pancuronium, vecuronium bromide, and atracurium besylate was determined in 12 experiments with each MR. In two other groups of 12 experiments each, with every MR, the cumulative dose response was determined after the addition of 10 μ M verapamil, or 2 μ M nifedipine to the bath. After >90% block had been established, four preparations of each group of 12 were washed with drugfree modified Krebs' solution; to four others we added 0.75 μ M neostigmine methylsulfate, and to four others we added 40 μ M 4-aminopyridine hydrochloride (4AP). We determined I₅₀ and I₉₀ concentrations of each MR alone and in the presence of verapamil or nifedipine from the computer-derived log dose-response regression lines. The maximal recovery of P after washout or the addition of neostigmine or 4AP was also noted.

In the in vivo experiments, rats were anesthetized with 35 mg/kg pentobarbital sodium plus 0.5 mg/kg urethane intraperitoneally injected (IP). One carotid artery and both external jugular veins were cannulated, the former for continuous recording of arterial blood pressure (BP), the latter for injection of drugs. The arterial line was kept open with the infusion of about 10 ml · kg⁻¹ · h⁻¹ 0.9% NaCl. Anesthesia was maintained with repeat doses of 10 mg/kg subcutaneous (SC) pentobarbital, as indicated. After induction of anesthesia, both sciatic nerves were exposed in the gluteal region, placed on bipolar platinum electrodes, and crushed with a heavy ligature, proximal to the electrodes. The distal tendon of both tibialis anterior muscles was dissected, separated from its insertion, and attached to FT03 transducers. Before the start of indirect stimulation, the optimal resting tension (25–30 g) was applied to the muscles. Stimulation and recording of P was identical to that described for the in vitro experiments. ED_{50} and ED_{90} μ g/kg doses of d-Tc, pancuronium, and vecuronium were determined from the cumulative log doseresponse regression lines in the absence of Caantagonists or 5 min after 0.4 mg/kg verapamil or 0.1 mg/kg nifedipine had been infused IV, over 10 min, in 1 ml/kg 0.9% NaCl. More rapid rates of administration of verapamil or nifedipine caused severe hypotension. In the experiments in which no Caantagonist was used, the same volume of 0.9% NaCl was infused over 10 min. After determination of the cumulative dose-response, spontaneous recovery of NM transmission was observed we recorded the recovery rate (time in minutes from the return of P from 25 to 75% of control), maximal recovery of P, and time to maximal recovery of P, measured from the time of development of the maximal effect of the last cumulative dose. It was difficult to obtain reproducible cumulative dose-response with atracurium in vivo. Determination of the dose-response with the individual dose method would have been too timeconsuming. Furthermore, the results of our in vitro studies indicated that it is unlikely that the interaction of Ca-antagonists with atracurium and with the other three MR would be qualitatively different. For these reasons atracurium was not included in the in vivo studies.

Heart rate (HR) and systolic, diastolic, and pulse pressures were also recorded before and at the end of the infusion, and also 5 minutes later, just before the start of the determination of the cumulative doseresponse. Twelve to 20 experiments were made with each of the three MR and with each of their combinations with verapamil or nifedipine.

Nifedipine is almost insoluble in water and is very photosensitive. For the in vitro studies, a 140- μ M nifedipine solution was prepared by dissolving 4.85 mg nifedipine in 100 ml of a solution consisting of 15 ml ethyl alcohol plus 15 ml polyethyleneglycol plus 70 ml distilled water. One ml of this solution added to the 70-ml bath resulted in a 2- μ M nifedipine concentration. Nifedipine solutions were prepared and the in vitro experiments were carried out in infrared light. In the in vivo experiments the nifedipine solution was protected from light during infusion by wrapping the syringe in tinfoil.

Data were statistically analyzed with analysis of variance (ANOVA) followed by Dunnett test or Student's t-test: P < 0.05 was considered statistically significant.

Results

In Vitro Experiments

It was determined in preliminary experiments that the addition to the bath of 1 ml of the solvent used for the preparation of the nifedipine solution had no measurable NM effect. Verapamil 10 μM or 2 μM nifedipine added to the bath 30 minutes before the start of the determination of the cumulative doseresponse of the MR had no effect on P. These concentrations of verapamil or nifedipine, however, caused a significant (ANOVA test) decrease of the I₅₀ and I_{90} of the four MR (Table 1). Isobolograms (Fig. 2) indicate that both Ca-antagonists potentiated the NM effect of MR. Verapamil decreased the I_{50} and I_{90} of d-Tc and vecuronium significantly more than nifedipine (Student's t-test). With pancuronium and atracurium, the differences between the effects of the two Ca-antagonists were not significant. After washout, with drug-free modified Krebs' solution, in the absence of Ca-antagonists, recovery rates and time to maximal recovery were significantly slower with *d*-Tc

Table 1. Influence of Verapamil or Nifedipine on the In Vitro Neuromuscular Potency and on the Recovery of Force of Contraction (P) After Washout*

				Recovery	parameters after wash	nout
Compounds					Time to maximal	Maximal
MR	Ca-antagonist	I_{50} (μM)	I_{90} (μ M)	Recovery rate (min)	recovery	recovery of P
-		0.47 ± 0.01	0.90 ± 0.03	12.3 ± 0.3 §	32.0 ± 0.3 §	93 ± 2
d-Tc	Verapamil†	0.25 ± 0.01	0.58 ± 0.03	11.0 ± 0.1	17.3 ± 0.3	75 ± 1
	Nifedipine	$0.34 \pm 0.03 \ddagger$	$0.69 \pm 0.03 \ddagger$	-1	34.0 ± 1.5	53 ± 6
	-	2.19 ± 0.07	3.73 ± 0.12	4.5 ± 0.4	12.0 ± 1.2	98 ± 3
Pancuronium	Verapamil	1.17 ± 0.08	2.63 ± 0.13	11.4 ± 0.9	16.9 ± 1.0	82 ± 3
	Nifedipine	1.32 ± 0.07	2.66 ± 0.13	8.9 ± 1.5	12.6 ± 1.9	81 ± 5
	_	3.77 ± 0.25	7.23 ± 0.44	4.6 ± 1.3	16.0 ± 1.0	101 ± 5
Vecuronium	Verapamil	1.97 ± 0.13	4.73 ± 0.22	10.4 ± 1.9	15.6 ± 1.5	78 ± 2
	Nifedipine	$2.63 \pm 0.21 \ddagger$	$6.60 \pm 0.42 \ddagger$		20.0 ± 2.2	73 ± 4
	_	11.47 ± 0.57	25.86 ± 1.27	5.8 ± 0.4	11.8 ± 1.4	92 ± 2
Atracurium	Verapamil	5.11 ± 0.72	14.21 ± 0.72		16.9 ± 1.1	60 ± 2
	Nifedipine	6.18 ± 1.05	15.61 ± 1.05		16.0 ± 1.7	64 ± 3

^{*}Rat phrenic nerve-hemidiaphragm preparation; modified Krebs' solution; stimulation with 0.1-second trains of 50-Hz impulses, every 20 seconds; I₅₀ and In values are mean \pm SEM of 12 experiments, recovery data are means \pm SEM of 4 experiments; verapamil 10 μ M, nifedipine 2 μ M. The I₅₀ and I₉₀ values of all four MR were significantly decreased by both verapamil and nifedipine (P < 0.001; ANOVA test). The I₅₀ and I₅₀ values of all four MR were significantly decreased by both verapamil and nifedipine on I₅₀ and I₉₀ values of the MR. Secovery rates (time for recovery of P from 25 to 75% of control) and time to maximal recovery, in absence of Ca-antagonists was significantly longer

||Maximal recovery (percent of control) was greater (P < 0.05 to 0.001; ANOVA test) with all MR in the absence of Ca-antagonists.

¶Recovery <75% of control.

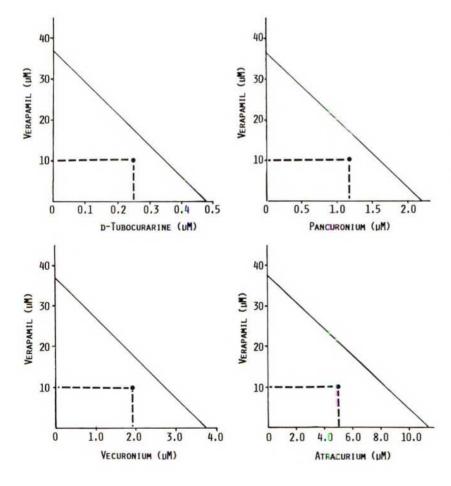


Figure 2. Isobolograms of the interaction of verapamil with d-tubocurarine, pancuronium, vecuronium, and verapamil. Diagonal solid lines (isobols) connect the I50 concentration point of verapamil on the ordinate with those of the muscle relaxants on the abscissa. Broken lines, perpendicular to the abscissa, start from the point of the I50 of muscle relaxants obtained in the presence of verapamil concentrations indicated by the starting point of broken lines perpendicular to the ordinate. Note that solid dots at the intersection of the broken lines are located left of the isobol. This indicates that the combined effect of verapamil and muscle relaxants is more than additive (potentiation) (17).

< 0.001; ANOVA test) with d-Tc than with other three MR]

Table 2. Influence of Verapamil or Nifedipine on Recovery Parameters After Neostigmine or 4-Aminopyridine (4AP)*

Compounds		Time to maximal reco	overy (min)	Maximal recovery of Pt	
MR	Ca-antagonist	Neostigmine (0.75 μM)	4AP (40 μM)	Neostigmine (0.75 μM)	4AP (40 μM)
	-	$6.3 \pm 0.3 \pm$	21.0 ± 1.00 §	68 ± 1	57 ± 2
d-Tc	Verapamil	4.5 ± 0.3	20.3 ± 0.3	65 ± 4	57 ± 5
	Nifedipine	5.3 ± 1.0	24.3 ± 0.3	39 ± 1	44 ± 4
	_	4.7 ± 1.5	29.7 ± 2.9	42 ± 3	64 ± 1
Pancuronium	Verapamil	6.0 ± 0.7	21.3 ± 0.9	36 ± 1	56 ± 1
	Nifedipine	6.7 ± 0.4	23.0 ± 1.0	50 ± 2	51 ± 4
		5.4 ± 0.9	32.3 ± 1.1	42 ± 2	59 ± 8
Vecuronium	Verapamil	6.9 ± 0.6	31.0 ± 3.2	36 ± 3	58 ± 2
	Nifedipine	6.1 ± 0.4	17.4 ± 2.8	31 ± 1	38 ± 2
		60.8 ± 6.5	85.8 ± 14.1	63 ± 5	108 ± 4¶
Atracurium	Verapamil	37.3 ± 8.6	31.0 ± 1.7 "	60 ± 2	92 ± 3 ¶
	Nifedipine	25.0 ± 2.9	23.5 ± 1.6	42 ± 6	44 ± 2

^{*}Experimental conditions as in Table 1.

Time to maximal recovery of P is longer than with other MR reversed by the same antagonist (P < 0.001; ANOVA test).

than with the other three MR (ANOVA test) (Table 1). Except for its combination with pancuronium, maximal recovery of P in the presence of nifedipine was <75% of control and, consequently, recovery rates could not be calculated. Maximal recovery of P was greater in the absence than in the presence of Ca-antagonists (ANOVA test).

The recovery parameters, without washout, after the addition of 0.75 μ M 4AP are summarized in Table 2. Recovery rates were not included in this table because maximal recovery of P after the addition of any of the two antagonists was only >75% after atracurium alone and verapamil plus atracurium. The significance of this observation will be discussed later. With *d*-Tc, pancuronium, and vecuronium, and with their combinations with either of the two Caantagonists, maximal recovery of P was <65% of control after reversal with neostigmine or 4AP. The time to maximal recovery, however, was always significantly less after neostigmine than after 4AP (Student's *t*-test).

In Vivo Experiments

The IV infusion of 0.4 mg/kg verapamil over 10 minutes decreased HR by about 10% of control (Table 3). Nifedipine 0.1 mg/kg infused over 10 minutes had no effect on HR. Verapamil decreased systolic BP by about 15% but, in 5 minutes, BP recovered close to control. Nifedipine had a delayed, moderate effect (about 7% decrease) on systolic BP. At the end of their infusion, both verapamil and nifedipine decreased diastolic BP by about 25%. Five minutes after the end of infusion, the effect of nifedipine on diastolic BP remained unchanged, but that of verapamil started to wear off. Both verapamil and nifedipine increased pulse pressure, nifedipine significantly more than verapamil (Student's *t*-test).

The IV infusion of 0.4mg/kg verapamil or 0.1 mg/kg nifedipine caused a <10% decrease of P. These doses of Ca-antagonists, however, significantly decreased the I_{50} and I_{90} (increased potency) of the MR investigated (ANOVA test) (Table 4). Nifedipine significantly

Table 3. Effect of Verapamil or Nifedipine on Heart Rate and Blood Pressure

	At end of infusion		5 minutes afte	r end of infusion
	Verapamil	Nifedipine	Verapamil	Nifedipine
Heart rate	90.2 ± 2.3*	103.9 ± 3.8†	91.3 ± 1.8	103.3 ± 3.9†
Systolic BP	85.7 ± 2.3	$100.0 \pm 3.7 \pm$	$97.2 \pm 2.4^{\circ}$	93.7 ± 2.6
Diastolic BP	73.7 ± 2.0	72.9 ± 3.1	$84.6 \pm 3.0^{\circ}$	$75.2 \pm 2.5 \dagger$
Pulse pressure	115.4 ± 5.0	$183.7 \pm 4.1 \dagger$	128.0 ± 5.2	159.1 ± 7.7†,

^{*}Mean ± sem of ten observations; all values expressed as percent of control.

[†]Percent of control.

[‡]All values are means ± sem of four experiments.

SExcept for attracurium and its combinations, maximal recovery of P was faster with neostigmine than with 4AP (P < 0.001; Student's t-test).

Maximal recovery of P after reversal with four AP is greater than with the other MR and their combinations with Ca-antagonists (P < 0.001; ANOVA test).

[†]Indicates significant difference between the effects of verapamil and nifedipine (P < 0.02; Student's t-test) at corresponding observation periods. ‡Indicates significant difference between the effects of verapamil or nifedipine (P < 0.02; paired t-test) at different observation periods.

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<u>Table 4</u>. Influence of Verapamil or Nifedipine on the In Vivo Neuromuszular Potency and on the Spontaneous Recovery of Force of Contraction (P)*

Compounds		ED ₅₀	ED∞	Posservani nata	Time to maximal	Maximal
MR	Ca-antagonist	$(\mu g/kg)$	(<i>µ</i> g_kg)	Recov∋ry rate (min)	(min) recovery	recovery of P (%)
-	_	34.1 ± 1.6	62.€ ± 1.0	5.1 = 0.3	13.2 ± 0.5	95 ± 2
d-Tc	Verapamilt	26.5 ± 1.1	50.≤ ± 1.5	4.9 = 0.3	12.7 ± 0.3	89 ± 1
	Nifedipine	22.9 ± 1.1	44 .€ ± 1.6	7.5 = 0.9	24.5 ± 1.8	98 ± 3
		118.9 ± 3.9	188.⊊ ± 4.0	3.8 = 1.2	15.7 ± 1.4	99 ± 1
Pancuronium	Verapamil	73.2 ± 6.6	121.7 ± 3.3	5.2 = 0.6	13.5 ± 1.7	88 ± 2
	Nifedipine	$57.8 \pm 4.8 \ddagger$	$101.2 \pm 2.5 \ddagger$	5.1 = 0.2	13.9 ± 1.1	90 ± 2
		220.0 ± 11.5	443.5 ± 10.8	2.1 = 0.1§	7.8 ± 0.3 §	96 ± 2
Vecuronium	Verapamil	124.9 ± 6.0	257.E ± 15.9	2.6 = 0.2§	7.2 ± 0.5 §	92 ± 1
	Nifedipine	137.0 ± 13.8	283.4 ± 27.1	2.7 = 0.2§	9.4 ± 0.7 §	89 ± 1

*Rat sciatic nerve-tibialis anterior preparation; stimulation parameter- as in Table 1; all values are means ± 5EM of six experiments. †The ED₃₀ and ED₉₀ values of the three MR were significantly decreased by both verapamil and nifedipine (P < 0.001; ANOVA test). †Indicates significant differences between the effects of verapamil and nifedipine on ED₅₀ and ED₉₀ of pancuronium (P < 0.001; ANOVA test). §Recovery rates and time to maximal recovery (see Table 1 for definitions) after vecuronium alone or in combination with verapamil or nifedipine were shorter than with d-Tc or pancuronium and their combinations with C_{2} -antagonists (P < 0.001; ANOVA test).

nificantly increased the NM effect of pancuronium more than did verapamil (Student's *t*-test). Sportaneous recovery of P was 88% of control or more, after the three MR alone or in combination with the two Ca-antagonists. Both recovery rates and times to maximal recovery were significantly more rapid after vecuronium and its combinations with Ca-antagonists than after *d*-Tc or pancuronium and their combinations (ANOVA test).

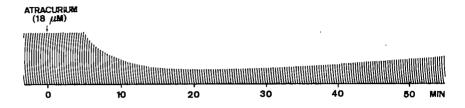
Discussion

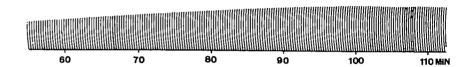
In agreement with earlier reports, concentrations (n vitro) or doses (in vivo) of verapamil or nifedip_ne which, alone, had little or no effect on P, increased the NM potency of MR. In vitro, the combined effect of verapamil or nifedipine with the four MR was greater than additive (Fig. 2). In rats the cardiovaszalar system is much more sensitive to Ca-antagonists than is the myoneural apparatus and the experimental animals did not tolerate high enough doses of these compounds to make possible the determination of their in vivo NM ED_{50} (1). Because of this, it cou d not be ascertained whether in vivo Ca-antagonists potentiate the NM effect of MR or their effect is additive. However, the degree of augmentation of the in vivo NM effect of MR by Ca-antagonists makes it probable that their combined effect is more than additive.

In vitro, maximal recovery of P after washout was less in the presence than in the absence of Ca-antagonists (Table 1). This indicates that Ca-antagonists are difficult to remove from the muscle (1) and suggests that these compounds may accumulate

in muscles of patients on Ca-antagonist maintenance therapy. Because the myoneural effects of Caantagonists cannot be antagonized by either neostigmine or 4AP (1), it may be difficult to reverse the NM effect of MR-Ca-antagonist combinations. Without washout, the addition of neostigmine or 4AP to the bath caused <75% recovery of P depressed by d-Tc, pancurorium, or vecuronium alone or in combination with Ca-antagonists (Table 2). The incomplete recovery of NM transmission after the addition of neostigmine was not unexpected. It has been reported that concentrations of neostigmine that completely antagonized the >90%-NM block in the rat phrenic nerve hemidiaphragm preparation stimulated at 0.1 Hz caused only partial reversal of the NM block in preparations stimulated with short trains of 50-Hz tetani (16). Recent experiments (18) indicate that the probable reason for the only partial antagonism of the NM block at physiologic, high stimulation rates is caused by the combination of two factors. The first of these is that during stimulation at 0.1 Hz, 10 seconds are available between stimuli for the mobilization of vesicular acetylcholine (ACh) and replenishment of readily releasable ACh stores. In contrast, during 50-Hz stimulation this time interval is reduced five huncredfold, to 0.02 second. The second factor is that MR inhibit the positive, nicotinic feedback mechanism for the mobilization of vesicular ACh (19). The combined effect of these two factors is that, despite the presence of cholinesterase inhibitors, the ACh concentration at the NM junction does not reach the level necessary for the competitive displacement of MR molecules from a large enough proportion of the cholinergic receptors of the postjunctional membrane

Figure 3. The course of the neuromuscular blocking effect of atracurium on the in vitro phrenic nerve—hemidiaphragm preparation. For experimental conditions, see Methods. Note that the >70% atracurium-induced neuromuscular block recovers spontaneously without washout close to its control value in <2 hours.





necessary for complete reestablishment of NM transmission.

Antagonism of the depression of P caused by atracurium plus nifedipine by neostigmine or 4AP was similar to that observed with the three other MR and with their combinations with verapamil or nifedipine. Unexpectedly, however, the time to maximal recovery of P, depressed by atracurium alone, was much longer after the addition of neostigmine or 4AP than that observed with the other MR or their combinations with Ca-antagonists. Maximal recovery of P depressed by atracurium alone or in combination with verapamil was also greater than that observed with the other MR or their combinations with Caantagonists (Table 2). It is conceivable that under our experimental conditions (ph 7.4, 37°C) the spontaneous breakdown of atracurium may have contributed to the slow but more complete recovery of the depression of P. To test the validity of this assumption 18 μM atracurium was added to three rat phrenic nerve-hemidiaphragm preparations (Fig. 3). This concentration of atracurium decreased P to 27.6 ± 2.4% of control (mean \pm sem) in 20.2 \pm 2.4 minutes. Without washout, spontaneous recovery started 2.3 ± 2.0 minutes after development of maximal effect and P recovered to 86.0 \pm 2.7% of control in 107.9 \pm 4.9 minutes. Because 4AP increases the contractile force of the muscle fiber (20), it is understandable that after atracurium alone, P increased to above control $(108 \pm 4\%)$.

In vivo doses of verapamil (0.4 mg/kg) or nifedipine (0.1 mg/kg) that caused little or no decrease of HR, moderate decrease of systolic BP, and about 25% decrease of diastolic BP (Table 3), significantly decreased ED₅₀ and ED₉₀ of the four MR (Table 4) (P < 0.001; ANOVA test). Spontaneous recovery of P after >90% depression produced by all drug combinations was more rapid and complete than in the in vitro studies (Table 4). This indicates that in rats, after

administration of doses of Ca-antagonists that are compatible with the functional integrity of the cardiovascular system, the augmentation of the NM effect of MR by Ca-antagonists, although significant, is short-lasting. This indicates that if the effect of Caantagonists on the cardiovascular and myoneural systems in rats and humans are similar, short-term administration of Ca-antagonists during anesthesia would temporarily increase the intensity of NM block but would not unduly prolong its duration. Furthermore, because after the administration of combinations of "safe" doses of Ca-antagonists and MR the proportion of NM block attributable to Ca-antagonists is <10%, reversal of residual block at the end of anesthesia to clinically acceptable levels should not be difficult. The results of the in vitro studies with combinations of MR and Ca-antagonists suggest that the interaction between these two groups of compounds may be different in patients on Ca-antagonist maintenance therapy. In these patients, Ca-antagonists may accumulate in the muscle and a greater proportion of the block may be attributable to Caantagonists. The myoneural effect of Ca-antagonists cannot be reversed by neostigmine or 4AP (1) and, as the results of this study indicate, the effect of MR-Caantagonists combinations can be reversed only partially by these compounds (Table 2). Consequently it can be expected that in some patients on maintenance doses of Ca-antagonists it may be difficult to reverse residual NM block at the end of anesthesia. Two such incidents have been reported already (21, 22). It would, however, require a carefully controlled prospective study to assess the incidence and severity of the difficulties that may be encountered in the reversal of the residual NM block in such patients. Meanwhile, the administration of MR should be carefully monitored in patients on preoperative Ca-antagonist therapy and the doses of MR should be limited to the

minimum that will provide satisfactory muscular relaxation.

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Does Diazepam Really Reduce the Cardiotoxic Effects of Intravenous Bupivacaine?

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GREGG RV, TURNER PA, DENSON DD, STUEBING RC, SELHORST CS, FORSBERG T. Does diazepam really reduce the cardiotoxic effects of intravenous bupivacaine? Anesth Analg 1988;67:9–14.

The effect of diazepam on the cardiovascular toxicity of bupivacaine was investigated in a rat model. Under chloral hydrate (400 mg/kg intraperitoneal) anesthesia, unilateral femoral venous and bilateral femoral arterial cannulae were placed for administration of drugs, for blood sampling, and for continuous qualitative monitoring of arterial blood pressure. Lead II ECG was continuously recorded and a tracheostomy performed to increase Fl_{O2} by use of a "T-piece." Four groups of 24 to 36 rats each were studied. All rats received IV bupivacaine 2 mg/kg, within 10 seconds. Group I, the control group, received only bupivacaine. Groups II and III received IV diazepam 0.2 mg/kg, or diazepam vehicle in an equivalent volume, respectively. Five minutes after this pretreatment, groups II and III

received IV bupivacaine 2 mg/kg. Group IV was given diazepam, 0.2 mg/kg, 30 seconds after injection of 2 mg/kg bupivacaine. A marked respiratory and metabolic acidosis occurred in all rats but was significantly worse in groups II and III. No rat in the study became hypoxemic. Serious arrhythmias (ventricular or supraventricular tachycardia) were noted in all groups, but the incidence was significantly higher in the group of rats given diazepam pretreatment than in the other three groups. It is concluded that IV diazepam 0.2 mg/kg given 5 minutes before administration of IV bupivacaine 2 mg/kg increases the incidence of serious cardiac arrhythmias. Second, this increase is not solely due to increased acidosis, because the rats receiving the vehicle (group III) developed equivalent acidosis but did not develop increased arrhythmias.

Key Words: ANESTHETICS, LOCAL—bupivacaine. TOXICITY—bupivacaine. BENZODIAZEPINES—diazepam.

Diazepam is widely used as a premedicant in patients scheduled for regional anesthesia. Diazepam reportedly protects patients from central nervous system (CNS) toxicity caused by local anesthetics by elevation of the seizure threshold (1–3). Diazepam has also been advocated in the treatment of CNS and cardiovascular system (CVS) toxicity resulting from accidental intravascular injections of local anesthetics (1–3). deJong and Bonin (1), for example, reported that "intravenous benzodiazepines commonly re-

duced the incidence of bupivacaine-induced ventricular arrhythmias." deJong and Davis (3) suggested that benzodiazepines were of value in treating bupivacaine-induced arrhythmias.

We studied the effects of diazepam on the CVS toxicity associated with an arrhythmogenic dose of intravenous bupivacaine in rats that were either pretreated with diazepam, or the vehicle in which diazepam is supplied or not pretreated at all.

Materials and Methods

The bupivacaine used was commercial 0.5% Marcaine (Winthrop-Breon). The diazepam was commercial Valium (5 mg/mL) (Roche) diluted to 0.01% (0.1 mg/ml) with 0.9% sterile saline for injection. The diazepam vehicle was generously provided by Roche Laboratories and was diluted in volumes equal to diazepam as above. For placebo injections, sterile 0.9% saline for injection was used.

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General Preparation

All animal care and experimental procedures were conducted in accordance with American Association for the Accreditation of Laboratory Animal Care (AAALAC) guidelines. Adult male Sprague-Dawley rats weighing 286 ± 47 g were used in this investigation.

The following procedure was used for all 126 rats. Rats were anesthetized intraperitoneally with chloral hydrate (400 mg/kg). After surgical anesthesia had been achieved, bilateral femoral artery and unilateral femoral vein cannulae (PE-50 tubing) were placed. One arterial line served as the sampling site for measurement of arterial blood gas tensions (ABGs) and drug concentrations, while the other was used for continuous "qualitative" (not calibrated to precise measurement) arterial blood pressure monitoring. The femoral venous cannula was used for the administration of drugs. A tracheostomy was then performed and the trachea intubated with a 14-Ga plastic vascular catheter cut to 1 cm in length below the hub. Rats were allowed to breathe spontaneously using a T-piece technique with 100% oxygen at 300 ml/min. Arterial blood pressure and ECG (lead II) were continuously recorded using a Tektronix model 412 monitor and a Gould model 220 brush recorder. Monitoring extended from a minimum of 5 minutes before and 10 minutes after injection of bupivacaine. If baseline ABG levels were not within the defined parameters or if the ECG was abnormal, the rat was replaced in the experimental protocol.

Electrocardiographic Interpretation

Electrocardiograms were recorded at a speed of 125 mm/sec for 10 seconds before bupivacaine injection and continued for 20 seconds afterward. Recordings for the remaining times during the experiments were conducted at a paper speed of 25 mm/sec. Interpretation of all recordings was based on previously published methods (4). Heart rates were measured before any pretreatment, immediately before bupivacaine injection, at the slowest rate after injection, and at the end of the experiment (10 minutes after bupivacaine injection). In all cases, 6-second periods were used for determination of heart rate.

Electrocardiograms were evaluated for the following life-threatening or "malignant" arrhythmias: third degree A-V block, supraventricular tachycardia (SVT), and ventricular tachycardia (VT). Of these, only VT and SVT were seen.

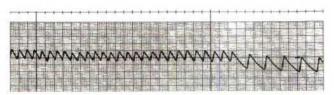
Blood samples (0.3 ml) were withdrawn for ABC measurements and 0.6-ml blood samples were with-

drawn when both ABG and bupivacaine measurements were made. All Pco_2 , Po_2 , and pH values were determined using a Radiometer model ABL-30 acid-base analyzer, which requires only 0.2 ml of blood. Serum bupivacaine concentrations were measured by gas chromatography (5). All rats had control ABGs (on 100% O_2 via t-piece) measured after the preparation described earlier. Acceptable baseline ABG levels were defined as $Pco_2 < 55$ torr, $Po_2 > 200$ torr, and BE > -7 mEq/L.

In the initial 12 rats in groups I and II, ABG and serum bupivacaine measurements were made 1 minute after bupivacaine injection. Because arrhythmias developed 70 to 100 seconds after bupivacaine injection and usually resolved within 3 minutes, arterial samples for ABG measurements in all subsequent rats were drawn 1.5, 2, and 3 minutes after bupivacaine injection. Subsequently, serum bupivacaine concentrations were measured in rats in groups I and II at the end of bupivacaine injection, i.e., as close to the "peak" levels as possible.

In all experiments, bupivacaine and a 0.25-ml saline flush were completed in <10 seconds. As noted earlier because of alterations in ABG sampling, groups I and II contain 12 more rats than groups III and IV. Group I (n = 36) rats served as controls and received only IV bupivacaine 2 mg/kg. Group II (n = 36) rats received IV diazepam 0.2 mg/kg, 5 minutes before IV bupivacaine 2 mg/kg. Group III (n = 24) rats received an IV diazepam vehicle in a volume equal to that given when diazepam was injected 5 minutes before IV bupivacaine 2 mg/kg. Group IV (n = 24) rats received IV diazepam 0.2 mg/kg, 30 seconds after IV bupivacaine 2 mg/kg. Group V (n = 6) rats received IV saline in volumes and at the same times as did the rats in group II.

All results are presented as means ± sp unless otherwise specified. Data were analyzed for normalcy of distribution using a Shapiro-Wilk W test to determine whether parametric or nonparametric analyses were appropriate. ABG data were analyzed by analysis of variance, using a one-within, one-between design, followed by a Scheffe critical value test for multiple comparisons at the P < 0.05 level to allow assessment of both intra- and intergroup differences. ABG data for group V were analyzed by Student's t test for repeated measures. Heart rates were analyzed using a one-way analysis of variance followed by the appropriate critical value test for multiple comparisons. The frequency of arrhythmias was evaluated using a test for significant differences between proportions or a Fisher's exact test where appropriate. Correlation of heart rate and ABG with malignant arrhythmias was determined using multiple linear



Typical early axis and conduction changes



<u>Figure 1</u>. Representative example of severe axis deviation and conduction changes that occurred immediately after injection of bupivacaine. The upper tracing is arterial pressure and the lower tracing is ECG lead II.

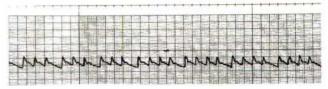
regression. Bupivacaine concentrations in control and diazepam pretreated rats were compared using a Student's t test for independent means. In all cases, a P value of <0.05 was considered the minimum level of statistical significance.

Results

The pH of the study solutions were the following: normal saline, 6.287 ± 0.096 ; 0.5% bupivacaine, 5.899 \pm 0.068; 0.01% diazepam, 5.700 \pm 0.011; and 0.01% diazepam vehicle, 5.563 ± 0.100. No significant differences in serum bupivacaine concentrations were found between the control and diazepam pretreatment groups either at the end of injection or at 1 minute postinjection. Serum bupivacaine concentrations for the control and diazepam groups at the end of injection were 38.9 \pm 17.3 and 40.4 \pm 22.2 μ g/ml, respectively. By 1 minute after injection, the bupivacaine concentrations had fallen to $1.84 \pm 0.88 \,\mu g/ml$ in the control rats and to $2.04 \pm 0.68 \mu g/ml$ in the diazepam-pretreated rats. There were no changes in sham rats (group V) in any of the variables measured.

Arrhythmias

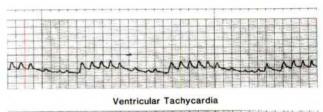
Severe axis deviations occurred in all 120 rats within 10 seconds after the bupivacaine injection. Figure 1 is representative of such changes. Malignant arrhythmias occurred in 6 of 36 control rats, 15 of 36 of the diazepam-pretreated rats, 3 of 24 of the rats pretreated with vehicle, and 3 of 24 of the rats given diazepam 30 seconds after bupivacaine injection. The frequency of arrhythmias in the diazepam pretreatment group was significantly greater than that in control rats, the vehicle group, and the diazepam



Type I 2" A-V block with variable intraventricular conduction block



<u>Figure 2</u>. Representative example of Type I second degree A-V block with intraventricular conduction block that appears to be rate-dependent. The upper tracing is arterial pressure and the lower tracing is ECG lead II.





<u>Figure 3</u>. Representative example of episodic ventricular tachycardia after administration of bupivacaine. The upper tracing is arterial pressure and the lower tracing is ECG lead II.

after bupivacaine group. Figure 2 demonstrates Wenckebach 2° A-V block with severe intraventricular conduction changes. The arterial blood pressure tracing aids in differentiating this from ventricular tachycardia (Fig. 3).

Heart rates were significantly higher in rats pretreated with diazepam (group II) (405 ± 29) than in either the control group (group I) (384 ± 51) or the vehicle group (group III) (372 ± 43) immediately before injection of bupivacaine. Diazepam pretreatment resulted in a significant increase in heart rate from 385 ± 39 beats/min before diazepam to 405 ± 29 immediately before bupivacaine injection. The minimum heart rates after injection of bupivacaine were significantly lower in both the diazepam (124 ± 40 beats/min) and vehicle (117 ± 31) groups when compared with the control group (171 ± 44). At the end of the experiment, heart rates, 318 ± 53 in the control group, 304 ± 92 in the diazepam group, and 302 ± 56 in the vehicle group were not significantly different.

No significant differences in pH, Pco₂, and base excess (acid-base status) were found in any of the

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Table 1. Arterial Blood Gas Tensions 1 Minute after Bupivacaine Injection*

	рН	Pco ₂ (mm Hg)	Po ₂ (mm Hg)	Base excess (mEq/L)
Before injection				
Controls (group I)	7.319 (0.021)	46.8 (5.7)	358 (130)	-2.5(2.0)
Diazepam (group II)	7.320 (0.027)	43.8 (7.8)	352 (81)	-3.7(2.9)
1 Minute after injection				\
Control (group I)	7.181 (0.030)	74.5 (9.5)	300 (136)	-3.5(2.3)
Diazepam (group II)	7.143 (0.04)†	77.5 (9.5)	262 (95)	-5.7 (2.1)+

*Mean (sp), n = 12 in each group.

⁺P < 0.025 when compared to control group 1 minute after injection.

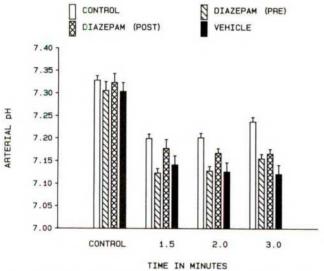


Figure 4. Changes in arterial pH after injection of bupivacaine.

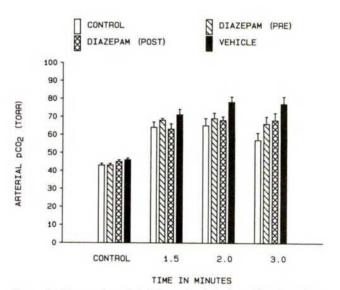


Figure 5. Changes in arterial Pco2 after injection of bupivacaine.

groups before the injection of bupivacaine. One minute after injection of bupivacaine, significant differences were detected in pH and base excess in the initial 12 rats in groups I and II. These data are summarized in Table 1.

Base excess, pH, and Po_2 decreased significantly and Pco_2 increased significantly above levels before injection of bupivacaine at all subsequent sampling times in all groups. No Po_2 value was <100 mm Hg in any ABG sample.

At 1.5 and 2 minutes after injection of bupivacaine, the pH was significantly lower in the groups pretreated with either diazepam or vehicle than in the control group. pH in the diazepam pretreated group was significantly lower than in the rats given diazepam after bupivacaine. At 3 minutes, pH for the control group was significantly higher than in the other three groups. These results are summarized in Figure 4.

Two minutes after injection of bupivacaine, the Pco₂ was significantly higher in the vehicle group than in the other groups. At 3 minutes, Pco₂ in the control group was significantly lower than that in the

other three groups. Values in the vehicle group were significantly higher than in either diazepam group (Fig. 5).

The Po₂ values in control group and in the group given diazepam after injection of bupivacaine were significantly lower than those in the group given diazepam before injection of bupivacaine and the group given diazepam vehicle for the control ABG. At 1.5, 2, and 3 minutes after injection of bupivacaine, the Po₂ in the groups pretreated with diazepam or vehicle was significantly higher than in the control rats. Po₂ in the vehicle group was also significantly higher than in rats given diazepam after bupivacaine injection (Fig. 6).

At 1.5 and 2 minutes after bupivacaine injection, base excess was significantly less in the group pretreated with diazepam than in all other groups. Base excess in the vehicle group was significantly lower than in either the control or in the rats given diazepam after injection of bupivacaine. At 3 minutes, base excess in the control group was significantly higher than in the other three groups (Fig. 7).

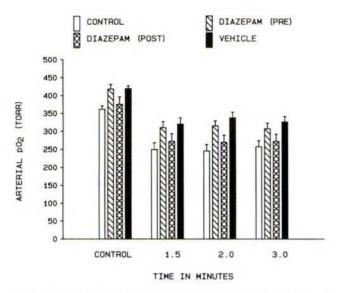
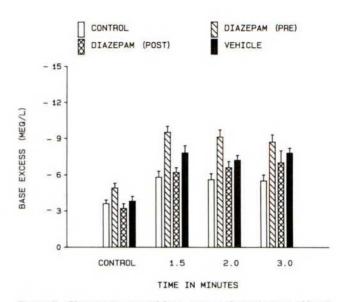


Figure 6. Changes in arterial Po₂ after injection of bupivacaine.



Contrary to previously published reports, a significant increase in bupivacaine-induced malignant arrhythmias was observed in rats pretreated with diazepam. The dose of diazepam (0.2 mg/kg) was chosen to approximate a human premedication dose and was lower than that used by deJong et al. (2 mg/kg) (1–3). It is possible that benzodiazepines exert a biphasic cardiovascular influence; a dose-response curve is needed to further elucidate the reasons for this apparent difference in experimental results.

The anesthetic selected (chloral hydrate) is known to produce minimal changes in CNS activity (6). The dose of bupivacaine (2 mg/kg) used in the present study was chosen because pilot studies in our laboratories demonstrated that this dose produced severe but reversible changes in cardiac conduction and rhythm (Gregg et al., unpublished results). Arterial bupivacaine concentrations at the end of injection of bupivacaine were in the range of those reported to be associated with bupivacaine cardiotoxicity in other animal models (7,8). One minute after injection, the serum bupivacaine concentrations had decreased to levels below those associated with cardiac arrhythmias (9). This decrease is indicative of rapid and extensive redistribution to highly perfused organs. The bupivacaine concentrations both at the end of injection and at 1 minute after bupivacaine injection were not significantly different in the control and in the diazepam-pretreated rats demonstrating that diazepam does not influence the rapid distribution phase of bupivacaine. This is in agreement with a previous report in monkeys (10).



<u>Figure 7</u>. Changes in arterial base excess after injection of bupivacaine.

Because many animals showed evidence of respiratory depression and ECG changes more than 1 minute after bupivacaine injection, a longer period of sampling for ABG measurements was instituted to examine the trend in acid-base status until the animals recovered. Bupivacaine injections resulted in both a metabolic and respiratory acidosis during the 3 minutes following injection of bupivacaine. The changes were not due to the volume, pH, or rate of bupivacaine injections themselves, because no alterations in acid-base status were noted in the sham group and the pH levels of the injectates were not particularly low. Although there were some significant intergroup differences in Po2 values, no group or single rat developed arterial hypoxia, thus ruling this out as a cause of the arrhythmias. Even though a mixed acidosis persisted 3 minutes after bupivacaine injection, most of the malignant arrhythmias had resolved and ECG traces were returning to their preinjection appearance by this time. The most severe metabolic acidosis occurred in the diazepam and vehicle pretreatment groups. However, there was not an increase in the frequency of malignant arrhythmias in the vehicle group when compared to the control group, suggesting that acidosis alone was not responsible for the occurrence of malignant arrhythmias. These observations are consistent with those reported in the dog (11) and in the guinea pig (12), but stand in contrast to results reported in sheep (8). Kasten and Martin (11) recently reported that sheep appear to be uniquely more sensitive to the cardiotoxic effects of bupivacaine than any of the numerous other animal models used for such studies. The interaction between acidosis and diazepam can-

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not be unequivocally eliminated by the present results. This possibility does, however, seem unlikely because no significant correlation(s) between heart rates, ABG changes, and malignant arrhythmias was detected.

The severe axis deviations that developed almost immediately after bupivacaine injection are consistent with early ECG changes reported with cardiotoxic doses of bupivacaine in the dog (13). The occurrence of multiple episodes of Wenckebach rhythms, as well as the rhythm disturbances similar to torsades de pointes, are also consistent with bupivacaine cardiotoxicity in the dog (13). Figure 2 demonstrates the rate-dependent intraventricular conduction delay that increases with each QRS complex until atrioventricular conduction is blocked. In almost all cases where it occurred, ventricular tachycardia occurred at the end of such a sequence, supporting the "reentry" hypothesis suggested by Kasten (13).

The 2.5-fold increase in frequency of malignant arrhythmias in rats pretreated with diazepam suggest that diazepam offers no protection from bupivacaine cardiotoxicity and, in fact, worsens the toxicity in the present model. The absence of differences between results in rats given diazepam after injection of burivacaine and results in control groups may indicate the lack of sufficient time for diazepam to occupy receptors and therefore diazepam did not influence the toxicity. These data are in disagreement with earlier studies which suggest that diazepam reduces ventricular arrhythmias associated with bupivacaine (1-3). This conflict in results may be due to differences 1) between the animal models, 2) in the dosage used to produce toxic responses with bupivacaine, or 3) in the evaluation of cardiotoxicity.

The present results raise several interesting questions concerning the use of diazepam as a routine premedicant for regional anesthesia. More studies designed to address the mechanism of the interaction between diazepam and bupivacaine (i.e., central or peripheral), as well as whether this interaction is limited to diazepam or whether such interactions exist for benzodiazepines in general, are needed to fully assess whether we should change our views cr

the use of benzodiazepines preceding or in conjunction with regional anesthesia.

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Cardiac Electrophysiologic Effects of Fentanyl and Combinations of Fentanyl and Neuromuscular Relaxants in Pentobarbital-Anesthetized Dogs

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ROYSTER RL, KEELER DK, HAISTY WK, JOHNSTON WE, PROUGH DS. Cardiac electrophysiologic effects of fentanyl and combinations of fentanyl and neuromuscular relaxants in pentobarbital-anesthetized dogs. Anesth Analg 1988;67:15–20.

The effects of fentanyl, both alone and in combination with pancuronium bromide or succinylcholine, on atrioventricular (AV) node and ventricular conduction times and refractory periods were studied. Twenty-four pentobarbitalanesthetized dogs were instrumented both with an intraaortic catheter to measure cardiac conduction times and, through a thoracotomy, with atrial and ventricular epicardial pacing electrodes to provide premature stimulation that would allow measurement of atrial and ventricular refractoriness. Fentanyl prolonged the RR interval in both low- (100 µg/kg) and high-dose (400 µg/kg) groups by 26 and 45%, respectively, and prolonged AV node conduction time by 28 and 25%, respectively. During atrial pacing at a rate sufficient to capture the atria, AV node conduction time lengthened in the low- and high-dose groups by 27 and 25%, respectively. Fentanyl also significantly lengthened

AV node effective and functional refractory periods and ventricular effective refractory periods in both groups. Pancuronium (0.1 mg/kg) administered after fentanyl shortened RR intervals in the low- and high-dose groups by 14 and 22%, respectively, and shortened AV conduction times by 18 and 20%, respectively, but did not restore all values to baseline. Pancuronium significantly shortened AV node refractory periods in the low-dose but not the high-dose group. When administered after fentanyl, succinylcholine (2 mg/kg) significantly shortened the RR interval in the low- and high-dose groups by 14 and 12%, respectively. Succinylcholine shortened AV node conduction slightly but without significance and had no effect on cardiac refractoriness. His-Purkinje conduction remained unaffected by any drug intervention. These data demonstrate that fentanyl depresses cardiac conduction; subsequent administration of pancuronium and succinylcholine partially reverses this effect.

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl. HEART—electrophysiology. NEUROMUSCULAR RELAXANTS—pancuronium, succinylcholine.

heart. Pancuronium bromide, in addition to main-

taining or increasing baseline heart rate in combina-

fentanyl and succinylcholine should result in reduc-

tion of heart rate. Using His bundle studies and the

premature stimulus technique, we investigated the

effects of fentanyl and combinations of fentanyl and

The combination of fentanyl, oxygen, and neuromuscular relaxants is a popular anesthetic technique for patients undergoing cardiac surgery. The vagotonic effect of fentanyl and the direct or indirect vagal effects of succinylcholine (1) cause deceleration of the

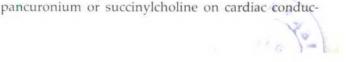
tion with fentanyl (2), also enhances atrioventricular (AV) node conduction (3). However, the effects of fentanyl and combinations of fentanyl and pancuronium or succinylcholine on AV node conduction and cardiac refractory periods remain undefined. The vagotonic effects of fentanyl may theoretically slow AV node conduction and prolong AV node refractoriness, and thus attenuating the enhancement of conduction by pancuronium. The combination of

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tion and refractoriness in pentobarbital-anesthetized dogs in a protocol simulating the induction sequence so often used in cardiac anesthesia.

Materials and Methods

Twenty-four mongrel dogs (13.5 to 27.0 kg) of either sex were anesthetized with an IV bolus of sodium pentobarbital (30 mg/kg) and intubated and ventilated with a Harvard 607 (TM) ventilator. No additional anesthetic was administered before fentanyl. After performing a right thoracotomy and pericardiotomy, we sutured epicardial atrial and ventricular pacing electrodes to the high right atrium and anterior surface of the right ventricle. A 6F tripolar His bundle catheter (USCI) was inserted through a left femoral cutdown and passed retrogradely into the ascending aorta and positioned during continuous monitoring with an ECG-His amplifier on an Electronics for Medicine VR-6 recorder until a stable His bundle electrogram was obtained. Positioning of the catheter in the area near the noncoronary cusp of the aortic root yields a stable His bundle and cardiac electrogram. In dogs, comparison of His bundle electrograms recorded from the aortic root and from a Hoffman-type plaque electrode sutured near the AV node and His bundle reveals virtually identical measurements (4). This technique also prevents confusion of an early right bundle potential with the His bundle potential.

For hemodynamic monitoring, we inserted a pulmonary artery catheter (primarily for volume measurements) percutaneously into the right external jugular vein and an arterial cannula into the right femoral artery through a right femoral cutdown. A Medtronics 5325 (TM) programmable stimulator delivering square wave impulses of 1.8-msec duration provided cardiac pacing and the VR-6 recorded data on photographic paper at 100 mm/sec paper speed. A lead II ECG was obtained and hemodynamic data were recorded on a Grass 7E polygraph. Temperature was maintained above 36°C with external heating pads. Serum potassium levels were maintained above 3.5 mEq/L with intravenous supplementation. Arterial Po2 was maintained above 70 mm Hg and arterial pH and Pco2 remained in the normal range with adequate ventilation and bicarbonate as required. Approximately 90 minutes elapsed from the time of anesthetic induction to completion of instrumentation before baseline studies.

At baseline and at each subsequent study period, we measured the following electrophysiologic data: spontaneous heart rate (RR interval); paced (PAH)

and unpaced atrial-His (AH) intervals; unpaced Hisventricle (HV) interval; atrioventricular node effective (AVERP) and functional (AVFRP) refractory periods; and retrograde ventricular effective refractory periods (VERP). The AH interval was measured from the beginning of atrial activity from the intraaortic catheter to the beginning of the His bundle potential. The HV interval was measured from the beginning of the His bundle potential to the earliest point of ventricular activation from the intraaortic catheter.

The basic cycle length for atrial and ventricular pacing was slightly shorter than the spontaneous cycle length and varied among dogs. However, we maintained the basic cycle length for pacing in each dog during refractory period measurement despite changes in the spontaneous cycle length. Refractory period determinations involved introducing increasingly premature stimuli after every eighth paced beat at a current twice that of the diastolic threshold. The current in milliamps remained unchanged after pacing threshold determinations for each refractory period measurement. As defined by Josephson and Seides (5), the AVERP represents the longest interval between the paced atrial impulse (A1) and the premature atrial impulse (A2) that fails to conduct to the His bundle; the AVFRP is the shortest interval between the paced His impulse (H1) and the premature His impulse (H_2) in response to any A_1-A_2 interval; the VERP corresponds to the longest interval between the paced ventricular stimulus and the premature ventricular stimulus that fails to capture the ventricle.

After baseline measurements, and approximately 2 hours after the pentobarbital, we divided the 24 dogs into two groups of 12, each receiving either 100 µg/kg (low dose) or 400 μg/kg (high dose) of fentanyl. (We thank Janssen Pharmaceutica, Piscataway, New Jersey for supplying fentanyl.) Intermittent infusion of Ringer's lactate solution maintained systolic blood pressure >100 mm Hg in both groups. After repeating data collection 5 minutes after fentanyl administration, each group was further subdivided into dogs given either IV pancuronium bromide 0.1 mg/kg (six dogs from the low-dose group and seven dogs from the high-dose group) or IV succinylcholine 2 mg/kg (six dogs from the low-dose group and five dogs from the high-dose group). Final studies were performed 5 minutes after injection of the neuromuscular relaxant, the entire data collection period lasting approximately 30 minutes (baseline to final study).

Using an SAS statistical program on a VAX 730 computer, we analyzed data by analysis of variance of repeated measures with P < 0.05 considered indicative of statistical significance. F-tests verified

A. EKG
$$AH = 75 \text{ msec}$$
B. AH = 110 msec
$$AH = 80 \text{ msec}$$

Figure 1. Intraaortic electrograms at 100 mm/sec paper speed from dog at (A), baseline (B) after $100~\mu g/kg$ fentanyl, and (C) after fentanyl and 0.1~mg/kg pancuronium.

that the variances were equal and that groups were not different before each drug intervention. The protocol was approved by the institutional Animal Care and Use Committee.

Results

Heart Rate and Conduction Times (Fig. 1 and 2)

Fentanyl (Table 1) 100 μ g/kg significantly prolonged RR, AH, and PAH intervals by 26, 27, and 46%, respectively, above baseline levels. Fentanyl 400 μ g/kg prolonged RR, AH, and PAH intervals by 45, 25 and 41%, respectively. Unpaced His-ventricle conduction did not change in either group. Pancuronium

(Table 2) significantly shortened RR, AH, and PAH intervals after fentanyl by 14, 18, and 32% in the low-dose group and 22, 20, and 26% in the high-dose group, respectively, but did not return these values to baseline. Succinylcholine (Table 3) significantly shortened the RR interval after low-dose and high-dose fentanyl by 14 and 12%, respectively (Fig. 2). Unpaced His-ventricle intervals were not affected by either pancuronium or succinylcholine. There was no significant difference in data between high-dose and low-dose groups at baseline or after drug administration.

Refractoriness

Fentanyl (Table 1) significantly prolonged AVERP and AVFRP in the low-dose group by 32 and 14%, respectively, and in the high-dose group by 35 and 17%, respectively. Retrograde ventricular effective refractory periods were significantly prolonged by fentanyl in both groups. High-dose fentanyl increased VERP more than did low-dose (P=0.02). Pancuronium (Table 2) significantly shortened AVERP by 27%, and AVFRP by 13% in the low-dose but not in the high-dose group. Pancuronium shortened VERP only in the high-dose group compared to postfentanyl (P=0.05). Succinylcholine (Table 3) had little effect on refractory periods, significantly shortening only AVFRP in the low-dose group (P=0.05).

Discussion

We designed this study 1) to examine the effects of high-dose fentanyl on AV node conduction and atrial

Figure 2. RR intervals at baseline (B), after fentanyl (F), and after pancuronium (P) or succinylcholine (S) in dogs given low (LD) and high doses (HD) of fentanyl. *P < 0.05 compared to baseline. †P < 0.05 compared to preceding value.

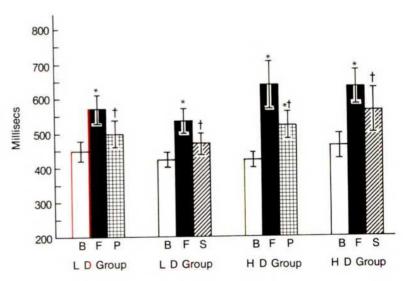


Table 1. Electrophysiologic Data (Mean \pm sem) Before and After Low (Group 1, n=12) and High Doses (Group 2, n=12) of Fentanyl

Interval	Fentanyl dose	Baseline (msec)	After fentanyl (msec)	% Change	P Value
RR	Low	435 ± 13.0	552 ± 26.9	0	37 77 78 74 75 75
	High	436 ± 13.0	635 ± 44.0	+26	< 0.01
AH	Low	69.0 ± 2.3	88.2 ± 3.0	+45	< 0.01
	High	72.0 ± 2.3	90.0 ± 4.0	+27	< 0.01
PAH	Low	73.0 ± 3.0		+25	< 0.01
	High	72.0 ± 3.0	107 ± 9.6	+46	< 0.01
HV	Low	22.8 ± 0.9	102 ± 5.0	+41	< 0.01
	High		23.5 ± 1.3	_	0.39
AVERP	Low	23.0 ± 0.5	23.1 ± 1.3	-	0.57
Litt		165 ± 4.0	218 ± 14.0	+30	0.01
AVFRP	High	179 ± 5.0	242 ± 2.8	+35	0.03
AVERE	Low	238 ± 6.0	273 ± 11.0	+14	0.01
VEDD	High	253 ± 7.0	298 ± 24.0	+17	0.03
VERP	Low	151 ± 4.0	155 ± 2.2	+2	0.01
	High	153 ± 4.0	163 ± 0.9	+6	0.01

Abbreviations: RR, RR interval; AH, atrial-HIS interval; PAH, paced atrial-HIS interval; HV, HIS-ventricular interval; AVERP, AV nodal effective refractory period; AVFRP, AV node functional refractory period; VERP, retrograde ventricular effective refractory period.

Table 2. Electrophysiologic Data (Mean \pm sem) After Fentanyl and Pancuronium in Dogs Given High (n=6) and Low Doses of Fentanyl (n=7)

Interval	Fentanyl dose	Baseline (msec)	After fentanyl (msec)	After pancuronium (msec)
RR*	Low	446 ± 28.3	570 ± 42.1‡	
Water Company	High	419 ± 24.9	637 ± 70.5‡	$497 \pm 41.8 \ddagger$
AH	Low	70 ± 3.3	92 ± 3.1‡	520 ± 38.1 § 75 ± 2.8 †
201710	High	73 ± 5.3	95 ± 5.6†	$76 \pm 5.4 \pm$
PAH	Low	72 ± 2.5	122 ± 16.28	83 ± 5.18
	High	72 ± 8.5	$108 \pm 8.5 \pm$	$80 \pm 9.8 \pm$
HV	Low	24 ± 1.2	25 ± 2.2	26 ± 2.2
A N Person on	High	22 ± 0.8	22 ± 0.8	20 ± 2.2 22 ± 0.8
AVERP	Low	170 ± 7.3	$250 \pm 22.6 \pm$	183 ± 13.8±
	High	185 ± 10.6	277 ± 43.8	216 ± 19.3
AVFRP	Low	243 ± 11.1	293 ± 19.18	255 ± 16.08
	High	258 ± 17.6	330 ± 35.4§	271 ± 22.6
VERP	Low	155 ± 14.9	159 ± 15.58	157 ± 16.0
	High	148 ± 3.6	160 ± 4.28	157 ± 16.0 154 ± 4.0 §

^{*}Abbreviations as in Table 1.

and ventricular refractoriness and, 2) to investigate the cumulative effects of large doses of fentanyl and subsequently administered neuromuscular blocking agent, both given according to anesthetic induction procedures widely used in cardiac surgical patients.

Although pentobarbital represented the only variable with no control in the present study, its levels should have declined significantly over the 1.5- to 2-hour interval between barbiturate administration and initiation of baseline measurements. Cox (6) demonstrated that hemodynamic parameters returned to normal within 15 minutes after 30 mg/kg of pentobarbital in dogs, although the heart rate remained elevated for up to 60 minutes. The rapid

sequence of experimental events—fentanyl administration, data collection, administration of either pancuronium or succinylcholine, and then final data collection—generally took less than 25 minutes, and simulated clinical induction of anesthesia. The sequence should have minimized any effect of decreasing barbiturate levels during the data-recording period; however, this effect cannot be ruled out.

We have demonstrated that 100 and 400 μ g/kg fentanyl significantly slow the heart rate and prolong the AH interval in dogs. The fentanyl-induced reduction in sinus node rate observed by others in both animal and human studies (2,7) is probably mediated by central vagal stimulation (8). Liu et al. (7) demon-

⁺P < 0.001.

[‡]P < 0.01.

 $[\]frac{1}{8}P < 0.05$. All comparisons involve preceding values.

<u>Table 3</u>. Electrophysiologic Data (Mean \pm SEM) After Fentanyl and Succinylcholine in Dogs Given High (n = 6) and Low Doses of Fentanyl (n = 5)

Interval	Fentanyl group	Baseline (msec)	After fentanyl (msec)	After succinylcholine (msec)
RR*	Low	421 ± 21.0	535 ± 36.0+	469 ± 30.5†
KK	High	461 ± 36.5	$633 \pm 49.4 \dagger$	$565 \pm 65.5 \ddagger$
AH	Low	67 ± 4.9	$84 \pm 5.0 \ddagger$	74 ± 4.6
Al I	High	70 ± 5.4	$85 \pm 4.7 \pm$	77 ± 2.0
PAH	Low	74 ± 9.3	92 ± 7.6 §	84 ± 6.2
IAII	High	71 ± 9.6	93 ± 6.2 §	82 ± 6.4
HV	Low	21 ± 0.7	21 ± 1.2	20 ± 1.3
114	High	24 ± 1.2	25 ± 1.8	25 ± 1.3
AVERP	Low	161 ± 6.0	185 ± 4.5 §	182 ± 4.4
AVER	High	168 ± 8.6	193 ± 16.7	181 ± 13.2
AVFRP	Low	234 ± 8.2	252 ± 4.4	$246 \pm 4.9 \ddagger$
AVINI	High	244 ± 10.3	254 ± 15.0	258 ± 13.6
VERP	Low	148 ± 5.8	$152 \pm 5.1 \ddagger$	153 ± 4.8
V LINI	High	159 ± 9.9	$167 \pm 10.2 \ddagger$	168 ± 10.0

^{*}Abbreviations as in Table 1.

strated significant declines in heart rate in dogs giving 50 μ g/kg fentanyl, with even greater significant reductions occurring after 500 μ g/kg. Dogs require higher doses for surgical anesthesia because of species variability (9).

We also observed that the PAH interval lengthens considerably more than does the spontaneous AH interval in response to fentanyl, despite no difference in PAH and AH intervals at baseline (Table 1). This greater slowing during pacing at shorter cycle lengths after fentanyl indicates significant depression of AV node conduction. Fentanyl may aggravate cardiac conduction defects in patients, especially those occurring in the AV node. Latson and Lappas (10) reported a case of transient second degree AV block occurring after a patient with preexisting first-degree AV block received 1.5 mg of fentanyl. Sufentanil may also cause cardiac conduction problems, including AV node block (11), bradycardia (11,12), and asystole (12).

Our data following pancuronium administration demonstrate the ability of this muscle relaxant to partially attenuate the fentanyl-induced slowing of the sinus rate and AV node conduction. Geha et al. (3) reported similar results, demonstrating a decreased AH interval when halothane-anesthetized dogs received pancuronium. The increased heart rate and possibly the enhancement of AV node conduction may have occurred secondary to either a vagolytic (13) or a sympathomimetic effect (14). Roizen et al. (15) demonstrated that humans responded to pancuronium by increasing heart rate and blood pressure and by reducing sympathetic tone through baroreceptor stimulation, resulting in decreased plasma

norepinephrine levels. Prior administration of atropine eliminated or reduced these effects of pancuronium, suggesting primary vagolysis. Unexpectedly, in the present study succinylcholine had similar effects of increasing heart rate (shortening the RR interval, Fig. 2) and decreasing the AH interval when administered after fentanyl. The generalized autonomic stimulation occurring after succinylcholine administration may account for this effect. Galindo and Davis (16) studied the effects of succinylcholine on cardiac excitability thresholds and hemodynamics before and after bilateral vagectomies and sympathectomy (total spinal anesthesia) in 20 rhesus macasus monkeys. Their series of experiments showed the presence of both parasympathomimetic and sympathomimetic effects with succinylcholine. In a state in which vagotonia is already prominent (after fentanyl), the sympathomimetic effects will likely become more evident (17). We cannot rule out an exaggerated response by fentanyl in these lightly anesthetized dogs with possibly enhanced sympathetic tone at baseline, although our baseline mean arterial blood pressure before fentanyl was normal $(96.3 \pm 2.8, n = 24)$. HV conduction times remained unaffected by fentanyl, pancuronium, or succinylcholine. This is in contrast to halothane, which appears to prolong HV conduction (18).

The refractory periods of the AV node and ventricle were significantly prolonged by both 100 and 400 μ g/kg fentanyl. Although the higher dose generally caused more prolongation than did the low dose, it was statistically significant only for VERP. Despite the ability of halothane, like fentanyl, to prolong AH intervals (18), Turner et al. (19) found that halothane

⁺P < 0.01.

 $[\]pm P < 0.05$

 $[\]S P = 0.06$. All comparisons involve preceding values.

shortened VERP in dogs during basal barbiturate anesthesia. This may represent an important difference between the two drugs or may represent differences in measurement techniques between their studies and ours. They measured refractoriness of the ventricular distal conducting system during pacing in the area of the His bundle, whereas we measured ventricular refractoriness during right ventricular pacing. We found that pancuronium significantly shortened the refractory period of the AV node only in the dogs receiving low-dose fentanyl. Succinyl-choline had little effect on refractory periods.

In summary, low and high doses of fentanyl in dogs slow heart rate and AV node conduction and prolong AV node and ventricular refractoriness. Pancuronium after fentanyl increases the heart rate and AV node conduction, but shortens only AV node refractoriness in dogs receiving low-dose fentanyl. Succinylcholine increases heart rate after fentanyl and increases AV node conduction nonsignificantly without affecting cardiac refractoriness. Both pancuronium and succinylcholine, when administered after large doses of fentanyl in pentobarbital-anesthetized dogs, have stimulating effects on heart rate and AV node conduction as compared to the depressant effects of fentanyl.

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Age-Dependence of the Dose-Response Curve of Vecuronium in Pediatric Patients during Balanced Anesthesia

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MERETOJA OA, WIRTAVUORI K, NEUVONEN PJ. Age dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 1988;67:21–6.

The effect of age on the log-based cumulative dose-response curve of vecuronium was determined in ten age groups of 80 pediatric patients ranging from neonates to adolescents during thiopental-fentanyl- N_2O/O_2 anesthesia. Neuromuscular block was recorded as the evoked thenar electromyographic response to train-of-four stimulation of the ulnar nerve (2 Hz at 20-second intervals). The dose-response curves were parallel to each other in all ten age groups studied. In neonates and infants, the ED95 of vecuronium was 47 \pm 11 (sd) $\mu g/kg$. This was significantly lower than

the ED $_{95}$ of 81 \pm 12 μ g/kg in children between 3 and 10 years of age (P < 0.01). In patients aged 13 years or older, the ED $_{95}$ was 55 \pm 12 μ g/kg, which did not differ from the neonatal and infant values but was significantly lower than the ED $_{95}$ of children between 3 and 10 years of age. The results indicate that the dose of vecuronium necessary for tracheal intubation is age-dependent. The individual ED $_{95}$ values varied between 22 and 103 μ g/kg. This suggests that an individually optimal dose of vecuronium can be administered to pediatric patients only if neuromuscular block is adequately monitored.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium. ANESTHESIA—pediatric.

Vecuronium is a nondepolarizing neuromuscular blocking agent with an intermediate duration of action devoid of cardiovascular side effects (1). In adults, there are fairly consistent data on the doses of vecuronium required to produce neuromuscular blockade (2–7). However, only a few studies have been conducted on the dose-response relations of vecuronium in pediatric patients (8,9). There are no pediatric studies of the dose-response relation of vecuronium during balanced anesthesia, and there are no data on the dose requirement of vecuronium in neonates. The aim of the present investigation was to determine the effect of age on the dose-response relation of vecuronium in pediatric patients from newborns to adolescents, during balanced anesthesia.

Methods

Eighty ASA I-II patients, from newborns to adolescents, who required neuromuscular relaxation for

their surgical procedure were studied. The study protocol was approved by the Ethical Committee of the Children's Hospital, University of Helsinki.

The patients were selected for the study on the basis of age. Ten groups, each with eight patients, were formed: patients <1 month; from 1 to <3 months; from 3 months to <1 year; from 1 to <2 years; from 2 to <3 years; from 3 to <5 years; from 5 to <7 years; from 7 to <10 years; from 10 to <13 years; and from 13 to <16 years of age. The patient characteristics are shown in Table 1. The patients had no medications or diseases known to affect neuromuscular function, and neither hepatic, renal or cardiovascular disease, nor abnormality of fluid and electrolyte balance.

The special characteristics of the newborns (patients <1 month) are shown in Table 2. All of them were being operated upon for clubfoot. The other operations in patients <1 year consisted of six endoscopies, five tenotomies, three hernial repairs, and two minor procedures. In older patients, 21 orthopedic operations, 11 hernial repairs, 9 endoscopic procedures, 9 corrections of hypospadia or phimosis, and 6 other surgical procedures were carried out.

Premedication was prescribed on the basis of din-

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Table 1. Patient Characteristics

Group	Age (yr)	Weight (kg)	BSA (m ²)
Under 1 month	$0.05 \pm .02$	3.8 ± 0.3	0.22 ± 1.1
1 month to <3 months	$0.14 \pm .04$	4.3 ± 1.2	$0.24 \pm .04$
3 months to <1 yr	$0.47 \pm .12$	7.7 ± 0.6	0.36 ± 02
1 yr to <2 yr	$1.53 \pm .34$	11.2 ± 1.8	0.49 ± 06
2 yr to <3 yr	$2.32 \pm .32$	13.6 ± 1.6	$0.58 \pm .04$
3 yr to <5 yr	$4.26 \pm .54$	17.4 ± 3.0	$0.71 \pm .06$
5 yr to <7 yr	$5.86 \pm .60$	19.9 ± 3.0	$0.82 \pm .06$
7 yr to <10 yr	$8.73 \pm .80$	29.4 ± 4.6	1.06 ± D8
10 yr to <13 yr	$12.05 \pm .95$	42.0 ± 7.4	1.33 ± 11
13 yr to <16 yr	$14.49 \pm .87$	51.6 ± 8.4	1.53 ± _14

Abbreviations: BSA, body surface area. Values are expressed as means \pm sp.

ical need. Patients <3 months of age did not receive any premedication. Patients aged 3 months to <1 year had rectal methohexital 15 mg/kg, the patients aged 1 to <3 years had flunitrazepam 0.08 mg/kg as an oral solution (most often supplemented with rectal methohexital), and the patients older than 3 years had oral flunitrazepam 0.08 mg/kg (maximum dose 2.0 mg) as premedication.

Induction of general anesthesia was carried out in every patient, after glycopyrrolate 5 μ g/kg, with fentanyl 3 μ g/kg and thiopental 2–4 mg/kg. Ventilation (nitrous oxide in oxygen 2:1) was controlled manually by mask to maintain end-tidal carbon dioxide between 5.0 and 5.5% (Normocap, Datex, Helsinki, Finland). No volatile inhalation anesthetic was used at any time during the study.

To monitor neuromuscular transmission by electromyogram (EMG), stimulating surface electrodes were attached over the ulnar nerve near the wrist with recording electrodes placed over the adductor pollicis muscle in the thenar eminence and on the proximal area of the middle finger. The forearm was placed in a dorsal splint to immobilize the hand and the fingers during the study. The neuromuscular monitor (Relaxograph, Datex, Finland) was calibrated when the patient was fully asleep and breathing N₂O in O₂, and the evoked electromyographic response to the train-of-four series of stimuli (at 2 Hz every 20 seconds) was recorded.

Vecuronium (4–16 mg of vecuronium diluted to 100 ml of 0.9% NaCl) was given in logarithm-based cumulative dose fashion. The first dose was $14 \,\mu g/kg$. The precalculated cumulative doses after successive increments were at regular intervals on a logarithmic scale (14, 22, 35, 56, and 89 $\mu g/kg$, respectively). The incremental doses were given when the EMG twitch responses had reached an unchanged level after the previous increment. The doses were given until 93–98% neuromuscular block was reached, after which tracheal intubation was performed. In some

Table 2. Characteristics of the Neonates

	Mean value	Range
Gestational age	39.6 weeks	37.7-41.6 weeks
Birth weight	3530 grams	2970-3850 grams
Apgar score at 1 and 5 min	9/10	9/9-10/10
Age at operation	17 days	11-27 days
Weight at operation	3760 grams	3330-4180 grams

cases, the last increment was smaller than the precalculated dose, to avoid >98% final neuromuscular block. The last increment was determined on the basis of individual responses when plotting the doseresponse curve during the study period. The mean values of actual cumulative doses were 14.0, 22.0, 35.0, 54.2, and 78.6 $\mu g/kg$.

The response of the first twitch of the train-of-four series was measured after every incremental dose. Individual dose-response curves were created by log-probit transformation (10), and the individual slope, ED_{10} , ED_{50} , and ED_{95} were determined by linear regression. Effective dose levels were calculated on the basis of both body weight (μ g/kg) and body surface area (μ g/m²). Body surface area was calculated using Boyd's formula (11).

Analysis of variance (ANOVA), with the Welch modification in cases of unequal variances, was employed for statistical analysis (BMDP Statistical Software 7D of 1987, Berkeley, California). The Tukey studentized range method was used to compare the slopes, and the mean ED $_{50}$ and ED $_{95}$ doses of the ten groups with each other; P < 0.05 was considered statistically significant. In the present study, a P value of 0.05 corresponds to P values of 0.0011 in the t-test, because there were ten age groups. Mean values are expressed with SEM.

Results

When the individual cumulative dose-response curves were plotted, 76 patients were given at least four doses and 42 patients five doses of vecuronium. The last two increments of vecuronium constituted 55–59% of the total cumulative dose. On average, the patients received 4.5 doses of vecuronium, and the time from the injection of the first dose to the last unchanged twitch height level was 9.6 minutes. The mean recording period of infants was 8.4 minutes; 19 of 24 were given four doses, and only 2 of 24 five doses of vecuronium. The mean recording period of older patients was 10.1 minutes; 15 of 56 were given four doses, and 38 of 56 five doses of vecuronium.

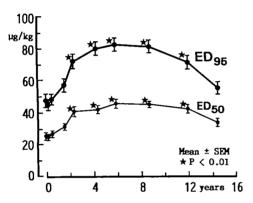
In all 80 patients, taken together, the first effective response in the dose-response curves represented 7.2

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Table 3. ED₅₀ and ED₉₅ of Vecuronium in Pediatric Patients during Balanced Anesthesia

<u> </u>				
Group	ED ₅₀ (μg/kg)	ED ₉₅ (μg/kg)	ED ₅₀ (<i>µg</i> /m²)	ED ₉₅ (μg/m²)
Under 1 month 1 month to <3 months 3 months to <1 yr 1 yr to <2 yr 2 yr to <3 yr 3 yr to <5 yr 5 yr to <7 yr 7 yr to <10 yr 10 yr to <13 yr 13 yr to <16 yr	25 ± 3 24 ± 2 27 ± 2 31 ± 2 $41 \pm 3^*$ $41 \pm 2^*$ $45 \pm 3^*$ $44 \pm 2^*$ $42 \pm 3^*$ 33 ± 2	48 ± 4 44 ± 4 49 ± 3 57 ± 5 72 ± 5* 80 ± 4* 82 ± 5* 81 ± 4* 71 ± 4* 55 ± 4†	420 ± 50 440 ± 50 560 ± 40 710 ± 60 $950 \pm 70^{\circ}$ $1000 \pm 40^{\circ}$ $1100 \pm 100^{\circ}$ $1310 \pm 80^{\circ}$ $1100 \pm 80^{\circ}$	800 ± 80 790 ± 90 1020 ± 60 1320 ± 130 $1680 \pm 110^{*}$ $1940 \pm 100^{*}$ $1990 \pm 160^{*}$ $2250 \pm 160^{*}$ $2220 \pm 110^{*}$ $1850 \pm 130^{*}$

Values are expressed as means \pm sem. *P < 0.05 compared with patients <1 month, <3 months, and <1 yr old. †P < 0.05 compared with patients <5 yr, <7 yr, and <10 yr old.



<u>Figure 1</u>. ED₅₀ and ED₅₅ of vecuronium in different age groups of pediatric patients under balanced anesthesia. There is a significant change in ED values from neonates to adolescents. The ED₅₀ and ED₉₅ values are highest in children between 2 and 13 years old.

 \pm 0.9% neuromuscular block, and the greatest level of neuromuscular block achieved averaged 95.6 \pm 0.2%. The slopes of the dose-response curves were not significantly different between the groups, the average slope being 6.7 \pm 0.1 probit/log. The time interval between successive increments of vecuronium averaged 2.2 minutes, without a significant difference between the studied groups. Train-of-four ratios decreased more rapidly than did the first evoked EMG twitch height, the decrease being fastest in patients between 3 and 10 years old. The train-of-four ratio at the time of 50% neuromuscular block was 42 \pm 2% in infants and 30 \pm 1% in children 3 to 10 years old (P < 0.01).

When the effective doses were calculated on the basis of body weight (μ g/kg), it was found that the ED₉₅ of vecuronium was significantly less in neonates and other infants than in patients >2 but <13 years old (Table 3). The ED₉₅ was identical in all patients <1 year (47 μ g/kg), but 73% greater in patients >3 but <10 years (P < 0.01) (Fig. 1). The ED₉₅ in patients >13

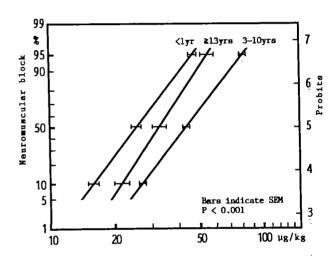


Figure 2. Dose-response curves of vecuronium in infants under 1 year of age, in children between 3 and 10 years old, and in adolescents 13 years of age or older. The dose of vecuronium that produces a 95% neuromuscular block in infants (ED₉₅) produces only about a 50% neuromuscular block in children, but a 90% neuromuscular block in adolescents. The curves are drawn by least square linear regression analysis of the mean ED₁₀, ED₅₀, and ED₉₅ of the groups.

years was close to the value in infants, but significantly less than the ED_{95} in children >3 but <10 years (Table 3, Fig. 1).

Figure 2 shows that the dose of vecuronium producing 95% neuromuscular block in patients aged <1 year (47 μ g/kg) produces only a 50% neuromuscular block in patients between 3 and 10 years old. A dose of 81 μ g/kg of vecuronium brings about a 95% neuromuscular block in the latter patients, but it is 1.7 times the ED₉₅ of infants (Fig. 2).

When the effective doses were calculated on the basis of body surface area (μ g/m²), the ED₉₅ of neonates and infants was significantly less than that of all patients 2 years old or older (P < 0.01) (Table 3). No side effects attributable to vecuronium were noticed in any patient.

Discussion

The cumulative logarithm-based incremental dose technique was used to plot the individual doseresponse curves. This was done even though some studies have shown that the cumulative technique leads to higher ED values of vecuronium than does the single-dose technique (3,6,12). However, in these studies the dose-response values were extrapolated far beyond the measured range (3,6), or the first dose in the cumulative-dose series did not produce the same level of neuromuscular block as did the same dose in the single-dose series (6,12).

Furthermore, in the cumulative-dose studies cited earlier, the first dose of vecuronium was the greatest (it constituted on an average >40% of the total cumulative dose), the last two doses constituted only 30% of the total dose, and the duration of the study period was between 14 and 18 minutes. This type of study design results in marked elimination of the first doses before the last measurements. Using the pharmacokinetic data on vecuronium (13-15), it can be calculated that the plasma concentrations of vecuronium at the time of last recorded twitch height in the cumulative dose studies cited above were lower than the plasma concentration that would exist at the time of maximum response if the same total dose were given as a single dose. Concurrently, the ED values were higher with these cumulative-dose techniques than with the single-dose technique (3,6,12).

In the present study, vecuronium was given in increments that produced cumulative doses at regular intervals on a logarithmic scale (14-22-35-56-89 μg/kg). In this way, the first dose constituted only 18-24% and the last two doses 55-59% of the total dose used, and the time between the first injection of vecuronium and the last recorded twitch height value averaged 10 minutes. On the basis of available pediatric pharmacokinetic data on vecuronium (16,17), it can be calculated that the plasma concentration of vecuronium at the time of our last recording was close to the plasma concentration that would exist 4 minutes after the same total dose had been given as one bolus dose. No plasma samples were taken in the present study and, hence, these calculations are only theoretical.

Fisher and Miller (9) found that the onset time of vecuronium (time from injection to maximum effect) averaged 1.5 minutes in infants and 2.4 minutes in children 1–8 years old. This relatively short onset time is corroborated by our finding that the unchanged response of the first evoked EMG twitch height was reached in an average of 2.2 minutes. This

short time in pediatric patients made it possible to create the dose-response curves within <10 minutes in the present study. The EMG recording technique and anesthesia induction were the same in every patient studied, but premedication differed between the study groups (see Methods). It is improbable, however, that this had an effect on our results, because patients over 3 years old had highest ED₉₅s and they were premedicated with flunitrazepam, which does not antagonize the effects of neuromuscular blocking agents. Furthermore, every patient received barbiturate (methohexital and/or thiopental) to induce sleep, followed by fentanyl and nitrous oxide in oxygen before the calibration of the neuromuscular monitor.

Goudsouzian et al. (8) found the ED $_{95}$ of vecuronium to be 60 μ g/kg and 45 μ g/kg in children aged 2 to 9 years and in adolescents aged 10–17 years, respectively. The average ED $_{95}$ values in the present study for both age groups were 33% higher, a result that can be attributed to the differences in anesthetic method (halothane vs. balanced anesthesia) and recording techniques (tension vs. EMG). Fisher and Miller found a tendency of ED $_{50}$ value of vecuronium to be higher in children than in infants or adults (9), a finding strongly supported by the present results. Because there are no other pediatric dose-response studies on vecuronium, no further comparisons can be made between the present and other existing pediatric data.

In the adult studies, in which the single-dose technique during balanced anesthesia has been used, the ED $_{90}$ of vecuronium has been found to be 40–44 μ g/kg (3,5,6). This is remarkably close to the ED $_{90}$ of 49 μ g/kg of our 13–16-year-old patients, although tension measurement has been used in the adult studies. Furthermore, Krieg et al. (2) administered a single dose of 36 μ g/kg of vecuronium to adults under balanced anesthesia, and recorded a 72% neuromuscular block with the tension technique. The ED $_{72}$ of our oldest patients is close to this dose, i.e. 39 μ g/kg (Fig. 2).

The present investigation shows that the ED $_{95}$ of vecuronium in all patients <1 year of age, including the neonates, is of the same magnitude (47 μ g/kg). The ED $_{95}$ level is the product of the distribution volume of vecuronium and its plasma concentration at the time of a 95% neuromuscular block. The muscle relaxants are distributed to the extracellular fluid volume (13–18). This volume is approximately 44% of body weight at birth and approaches the adult value of 22% at 1 year of age (19). Therefore, in neonates the neuromuscular block is probably reached at a

much lower total plasma concentration of vecuronium than in older infants. Fisher et al. (20) showed this to be the case with *d*-tubocurarine. In addition to the immaturity of the neonatal neuromuscular function, the low serum protein levels in neonates may result in diminished protein binding and increased free fraction of vecuronium in plasma and, therefore, neonates may need lower total plasma concentration of vecuronium than do older infants.

In children between 2 and 13 years of age, the ED₉₅ of vecuronium was 65% greater than that in infants (77 vs. 47 μ g/kg). If the protein or tissue binding of vecuronium is greater in rapidly growing children than in infants, they need higher total plasma concentration of vecuronium to reach the same level of neuromuscular block. This may be the reason why, in the present study, the ED₅₀ and the ED₉₅ values of vecuronium were higher in children than in infants. Fisher et al. (16,20) have, indeed, found that the steady-state plasma concentration of vecuronium resulting in a 50% neuromuscular block is higher in children than in infants. The smaller ED₉₅ of vecuronium in infants compared with children explains why a constant dose of vecuronium has longer neuromuscular blocking effect in infants compared with children (9).

The ED₉₅ of vecuronium in adolescents \geq 13 years of age was significantly less than the ED₉₅ in children between 3 and 10 years old (55 vs. 81 μ g/kg), but did not differ from the ED₉₅ in infants (47 μ g/kg). The equal ED₉₅ in infants and adolescents can be attributed to different distribution volumes and plasma concentrations, which may counterbalance each other (16,20). This means that neonates and infants need the same dose of vecuronium (μ g/kg) as adolescents to attain the same level of neuromuscular block. In contrast, children need a significantly greater dose to attain a comparable neuromuscular block.

When vecuronium is used for tracheal intubation in pediatric patients, ≥90% neuromuscular block is necessary for optimal conditions during balanced anesthesia. This means that at least an ED95 dose has to be administered. In the present study, this dose varied between 22 and 68 µg/kg in neonates and infants, and between 56 and 103 μg/kg in children and adolescents. If an initial dose of 100 μ g/kg of vecuronium is administered to infants, this is 1.5-4.5 times the ED95 calculated in the present study, and may result in profound neuromuscular block lasting for more than 1 hour. The dose of 100 μ g/kg is only 1.0–1.8 times the ED₉₅ in children between 3 and 10 years old. In these children this dose does not maintain a surgical neuromuscular block for longer than 15-30 minutes.

In clinical situations, a peripheral neurostimulator or a more sophisticated EMG- or tension-monitor should be used in every pediatric patient given vecuronium because neuromuscular responses are so highly variable among individual patients.

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Awakening Concentrations of Isoflurane Are Not Affected by Analgesic Doses of Morphine

Jeffrey B. Gross, MD, and Christian M. Alexander, MD

GROSS JB, ALEXANDER CM. Awakening concentrations of isoflurane are not affected by analgesic doses of morphine. Anesth Analg 1988;67:27–30.

A randomized, double-blind study was performed to determine how morphine 0.1 mg/kg IV, or placebo administered 80 ± 11 ($\overline{X}\pm sE$) minutes before the end of surgery affect recovery from isoflurane/oxygen anesthesia. End-tidal isoflurane remained constant at $1.10\pm0.02\%$ ($\overline{X}\pm sE$) in both groups intraoperatively, and no other anesthetics were given after the administration of the morphine or placebo. Duration of anesthesia did not differ significantly between the morphine (172 \pm 7 minutes) and placebo (163 \pm 18 minutes) groups. Times from discontinuation of isoflurane

until eye-opening in response to verbal command were similar in the morphine (19 \pm 2 minutes) and placebo (22 \pm 3 minutes) groups. At the time of eye-opening, end-tidal isoflurane concentrations did not differ between subjects receiving morphine (0.20 \pm 0.02%) and placebo (0.18 \pm 0.01%). It is concluded that the awakening concentration (MAC-awake) during recovery from isoflurane anesthesia is approximately 0.19% and is not affected by analgesic doses of morphine.

Key Words: ANALGESICS, NARCOTIC—morphine. ANESTHETICS, VOLATILE—isoflurane. POTENCY, ANESTHETIC—MAC. POTENCY, ANESTHETIC—MAC-awake.

The alveolar concentration of an anesthetic at the time patients are first able to open their eyes in response to verbal command during recovery from anesthesia is called MAC-awake. During recovery from halothane, fluroxene, and methoxyflurane anesthesia, MAC-awake ranges from 0.33 to 0.5 times the conventionally determined MAC for these agents (1). However, there are no published MAC-awake data for isoflurane, despite its increasing popularity. We designed the present randomized double-blind study to assess MAC-awake during recovery from isoflurane anesthesia (with inspired isoflurane concentrations near zero) and to determine if an analgesic dose of morphine significantly affects MAC-awake or prolongs emergence from anesthesia.

Methods

Fourteen ASA I or II patients, 21 to 59 years old,

scheduled for general, orthopedic, or oral surgery, consented to participate in this study, which was approved by our Human Studies Committee. They fasted for at least 8 hours before surgery and received no sedative or narcotic premedication (glycopyrrolate, which does not cross the blood-brain barrier, was administered at the discretion of the attending anesthesiologist). For each subject, we inserted an intravenous cannula and established ECG and noninvasive blood pressure monitoring. Then, induction of anesthesia and paralysis with thiopental 5 mg/kg and succinylcholine 1 mg/kg was followed by tracheal intubation. An Allegheny International SARA (R) mass spectrometer system, calibrated with laboratory standard gases within 1 hour of each study, continually measured inspired and end-tidal oxygen, CO2, and isoflurane concentrations. For maintenance of anesthesia we used isoflurane in oxygen, maintaining end-tidal isoflurane concentrations between 1.08 and 1.12%. Mechanical ventilation (10 breaths/min) kept patients' end-tidal CO₂ tensions between 23 and 27 mm Hg. If additional anesthesia was required, we administered small doses of thiopental (totaling 1.7 \pm 0.3 mg/kg, $\overline{X} \pm sE$) or transiently increased the

isoflurane concentration; however, for at least 1 hour

before the end of surgery we administered no thio-

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pental and maintained isoflurane concentrations of $1.10 \pm 0.02\%$. If surgically indicated, we administered nondepolarizing muscle relaxants, completely reversing them with neostigmine and glycopyrrolate before discontinuing the inhalation anesthesia. Approximately 1 hour before the end of surgery, patients received either morphine 0.1 mg/kg or an equal volume of saline placebo IV in a double-blind fashion.

When surgery was complete, we discontinued isoflurane administration, flushed the circle breathing system with oxygen, increased O2 inflow to 12 L/min, and continued mechanical ventilation (endtidal CO₂ tension, 25 ± 2 mm Hg), so that morphineinduced ventilatory depression would not slow the elimination of isoflurane and affect its brain-bloodalveolar gradients. To standardize the stimulus for awakening, we used an endless-loop tape played through occlusive headphones, which instructed patients to open their eyes. The tape played for 20 seconds each minute, to avoid acclimating the patients to the aural stimulus. When patients opened their eyes, we recorded the end-tidal isoflurane concentration as well as the time elapsed since discontinuation of isoflurane (wake-up time). We then extubated the patients as usual and transported them to the recovery room.

To compensate for the known effect of age on an esthetic requirements, we computed the ratio of MAC-awake to the age-adjusted isoflurane MAC (2) for each patient. We determined confidence limits for MAC-awake and the MAC-awake:MAC ratio in the usual manner. One-way analysis of variance compared variables between groups; multiple linear regression determined if the thiopental dose affected MAC-awake or wake-up time. P < 0.05 indicated statistical significance.

Results

Patient ages, duration of isoflurane administration, induction and total doses of thiopental, and time from administration of morphine or placebo until the end of surgery did not differ significantly between groups (Table 1). For patients receiving morphine, MAC-awake ($0.20\pm0.02\%$, $\overline{X}\pm sE$) did not differ significantly from that in patients receiving placebo ($0.18\pm0.01\%$); the MAC-awake:age-adjusted MAC ratio also did not differ between the morphine (0.16 ± 0.02) and placebo (0.15 ± 0.01) groups. Pooling the data resulted in 95% confidence limits for MAC-awake of $0.19\pm0.03\%$, and for the MAC-awake: MAC ratio of 0.15 ± 0.02 . Time from the discontinuation of isoflurane until eye-opening (wake-up time)

Table 1. Summary of Patient Data

	Placebo	Morphine
No. of patients	7	7
Age (yr)	34.4 ± 4.4	34.9 ± 4.2
Total duration of isoflurane administration (min)	163 ± 18	172 ± 7
Total thiopental dose (mg/kg)	7.1 ± 0.4	6.3 ± 0.7
Time from morphine or placebo until isoflurane wears off (min)	51 ± 9	80 ± 11
Wake-up time (min)	21.9 ± 3.1	19.4 ± 2.4
MAC-awake (%)	0.18 ± 0.01	0.20 ± 0.02
MAC-awake:MAC ratio	0.15 ± 0.01	0.16 ± 0.02

Values are means \pm se. There are no significant differences between the groups.

was no different in the morphine (19 \pm 2 minutes) and placebo (22 \pm 3 minutes) groups. Neither MAC-awake nor wake-up time correlated significantly with the total thiopental dose. As determined from the mass spectrometer record, end-tidal isoflurane concentrations were declining at a rate of 0.008 \pm 0.0001%/min at the time when patients first opened their eyes to command.

Discussion

With the increasing availability of on-line anesthetic gas analysis (mass spectrometer, infrared, crystal adsorption, Raman scattering), our ability to quantitate anesthetic gases during anesthesia is enhanced. Knowledge of the concentration of an anesthetic associated with eye-opening enables us to time more accurately the discontinuation of anesthesia, allowing patients to open their eyes as the dressings are applied. Ideally, the "awakening concentration" of an anesthetic should be determined in the brain. Because this is impractical, we can apply techniques similar to those used for determination of MAC, where end-tidal gas concentrations are used to approximate brain partial pressures.

MAC-awake is the alveolar concentration of anesthetic present when patients can respond to verbal command by opening their eyes during emergence from anesthesia; it is a maximum concentration, because patients will open their eyes when concentrations are equal to or less than MAC-awake. This is in contrast to MAC, which is a minimum concentration, because patients do not respond to skin incision when concentrations are equal to or greater than MAC.

Stoelting, Longnecker, and Eger determined MAC-awake in two ways: one of these was a steady state method, in which the investigators determined

responsiveness to verbal commands after holding anesthetic concentrations constant for 15 minutes. The other method allowed "spontaneous recovery" from anesthesia. "In these patients, the inspired anesthetic concentrations were zero, and no attempt was made to hold alveolar concentrations constant" (1). We chose the latter method because it more closely approximates clinical situations, in which patients are awakened most quickly by reducing the inspired anesthetic concentration to zero.

Determinations made by the spontaneous recovery method may underestimate the MAC-awake within the brain because alveolar anesthetic tensions are necessarily lower than cerebral tensions during anesthetic washout (1,3). However, this discrepancy is greatest immediately after the anesthetic is discontinued (3) and decreases as the alveolar concentration curve "flattens out." In fact, with methoxyflurane, the values of MAC-awake determined by the two methods do not differ; because of its high blood and tissue solubility, methoxyflurane concentrations decrease slowly throughout the recovery from anesthesia (4). By maintaining end-tidal isoflurane concentrations of 1.1% until the end of surgery, we ensured that awakening would occur at a time when isoflurane concentrations were on the flat part of the washout curve (v.s.). In fact, previous washout data for isoflurane suggest that under the conditions of our study, end-tidal isoflurane concentrations underestimated arterial tensions by <0.08%

Nonetheless, our estimate of 0.15 for the MACawake:MAC ratio is appreciably lower than the value of 0.33 reported by Stoelting et al. (1) during spontaneous decreases in the alveolar concentration of halothane or fluroxene. There are several possible explanations for this discrepancy. First, in the previous study, patients breathed spontaneously during the washout of anesthetics, whereas in our patients ventilation was controlled. This ensured that end-tidal gas was more consistently representative of alveolar gas, and eliminated ventilatory pattern as a potential source of differences in MAC-awake between the morphine and control groups. However, by lowering arterial CO2 tensions, controlled ventilation may have decreased cerebral blood flow, thereby increasing the brain to alveolar isoflurane tension gradient. A second factor is that we obtained end-tidal gas samples every 30-60 seconds and recorded MACawake when patients opened their eyes. At this time, end-tidal isoflurane concentrations were decreasing by <0.01%/min. Conversely, Stoelting's group obtained samples at 3-5 minute intervals, and reported MAC-awake as the value "midway between the alveolar concentration at the initial response and the anesthetic concentration of the last sample obtained prior to response" (1). They did not report the rate of decline of anesthetic concentrations; however, they found that under these conditions, differences between blood and alveolar anesthetic concentrations were small. Additionally, in the Stoelting study, "the patient was asked frequently to open his eyes"; the intensity and frequency of the wake-up stimulus was not specified. In contrast, to ensure consistency, we used a standard aural stimulus delivered through occlusive headphones; tactile stimulation was not permitted. Like Stoelting et al., we required patients to open their eyes to command; we did not accept involuntary or reflex patient movement as evidence of "awakeness." Finally, unlike Stoelting's subjects, our patients received thiopental for induction of anesthesia; although none was administered for at least 1 hour before the end of our surgery, residual low concentrations of thiopental may have slightly decreased our MAC-awake values.

We designed our study to minimize error introduced by the time-shared mass spectrometer system. Severinghaus's group documented a 10–90% rise time of 0.28 second for halothane with a time-shared mass spectrometer system (6) similar to the one we used for this study. We have shown (unpublished observations) that, provided expiratory times exceed 2 seconds, end-tidal isoflurane measurements by our system are within 3% of their steady state value. Because we controlled respiration rate (10 breaths/min; I:E ratio, 1:2), our patients' expiratory times were about 4 seconds; this minimized the error caused by "smear" as the sample was transported from the airway to the analyzer.

Why did morphine fail to decrease MAC-awake? One possibility is that too much time (80 \pm 11 minutes) may have elapsed between morphine administration and MAC-awake determination. However, Hug et al. (7) found that respiratory depression (as an index of CNS activity) peaks 60-90 min after IV morphine. Differences in thiopental doses between the groups could have affected the results. Although patients in the placebo group received slightly more thiopental than did those in the morphine group, this difference was not statistically significant, and multiple regression revealed no evidence of an inverse relation between thiopental dose and MAC-awake (slope + 0.02, P > 0.10). Furthermore, because we gave no thiopental after the morphine or placebo was administered, this difference was strictly random: i.e., patients in the placebo group did not receive additional thiopental to compensate for the absence of morphine. By controlling ventilation, we ensured identical anesthetic washout in the placebo and morphine groups. Had we allowed patients to breathe spontaneously, those who received morphine probably would have awakened more slowly because of morphine's respiratory depressant effects. Finally, morphine may provide more analgesia than sedation: even after 1 mg/kg some patients respond to verbal stimuli despite profound analgesia (8). Therefore, morphine might be expected to have less of an effect on MAC-awake, which involves response to a verbal stimulus, than on MAC, which assesses response to a painful stimulus.

In conclusion, the MAC-awake for isoflurane is 0.19% (or 0.15 × MAC) during emergence from surgical anesthesia under clinical conditions (no inspired isoflurane, controlled ventilation). This figure, as well as the time required for patients to "wake up" after isoflurane is discontinued, appears to be independent of the administration of analgesic doses of morphine (0.1 mg/kg IV) approximately 1 hour before the end of surgery.

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The Anesthetic Contribution of Magnesium Sulfate and Ritodrine Hydrochloride in Rats

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THOMPSON SW, MOSCICKI JC, DIFAZIO CA. The anesthetic contribution of magnesium sulfate and ritodrine hydrochloride in rats. Anesth Analg 1988;67:31–4.

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The anesthetic effects of the tocolytic agents, magnesium sulfate and ritodrine hydrochloride, were investigated by determining their effect on the minimal alveolar anesthetic concentration (MAC) of halothane in male and in pregnant and nonpregnant female rats. Magnesium and ritodrine were administered by continuous intravenous infusion to mechanically ventilated rats anesthetized with halothane. The tail-clamp technique was used to establish the MAC of halothane before and then again during the infusion of either magnesium or ritodrine. Ritodrine produced no change in halothane MAC. Increasing magnesium dosages and magnesium plasma levels were associated with nonli-

near reductions in halothane MAC that were unrelated to sex or pregnancy. The alveolar halothane MAC concentration in pregnant rats (0.85 \pm 0.02) was not significantly different from the halothane MAC in nonpregnant female or male rats. At the highest plasma magnesium concentrations (15.8 \pm 1.57 mg/dl) achieved in the pregnant rats, the alveolar halothane MAC was 0.36 \pm 0.13, a 61.6% reduction in MAC. The anesthetic effects of magnesium were not attributable to cardiovascular, respiratory, or neuromuscular depression. Major decreases in blood pressure occurred only in the pregnant rats with the highest magnesium concentrations.

Key Words: POTENCY, ANESTHETIC—MAC. ANESTHETICS; VOLATILE—halothane. IONS—magnesium. ANESTHESIA—obstetric.

Magnesium sulfate (MgSO₄) is used in obstetrics to inhibit premature labor and in the therapy of preeclampsia-eclampsia. Ritodrine hydrochloride, a synthetic sympathomimetic amine, is also used to suppress premature labor. Although MgSO₄ therapy results in sedation and ritodrine therapy does not, there is conflicting data as to whether magnesium has an anesthetic effect. Meltzer and Auer (1) initially reported CNS depression with IV MgSO₄ in rabbits, and later Peck and Meltzer (2) employed IV MgSo4 as the sole "anesthetic" in humans. Aldrete et al. (3) concluded, however, that magnesium has no direct general anesthetic properties in dogs but produces "sleep-like" effects secondary to cardiac depression and hypoxia. Somjen et al. (4) were unable to demonstrate analgesia in humans despite IV MgSO4 administration to plasma levels of 15 mEq/L (15 mEq/L ≅ 18.2 mg/dl). Alternatively, drugs that affect CNS catecholamine levels (methyldopa, reserpine, amphetamine, cocaine) produce changes in anesthetic requirements (5). It is not known whether the sympathomimetic amine, ritodrine, contributes to anesthesia. This study was undertaken to determine the anesthetic effects of MgSO₄ and ritodrine hydrochloride after IV administration in rats and to determine if the anesthetic effect was related to either animal sex or pregnancy.

Methods

Halothane MAC (minimal alveolar concentration) and changes in halothane MAC were established as previously reported (6). Thirty-four Sprague-Dawley rats were classified into three groups: male, female, and rats at term pregnancy. The rats were anesthetized with halothane in oxygen and intubated. Ventilation was controlled with a Harvard animal respirator. A femoral artery and vein were cannulated, and arterial waveform, as well as the ECG, were monitored continuously. Arterial blood gas tensions were maintained within physiologic range. Rectal temperature was also maintained within physiologic range using a blanket and radiant light source. Alve-

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Table 1. Anesthetic and Physiologic Effects of Varying Mg²⁺ Plasma Levels

	**		Blood pressure		
	Plasma levels	Heart rate	(mm	Halothane	
n	Mg^{++} (mg/dl)	(beats/min)	Hg)	MAC (%)	
Group 1 (control)					
9 (P)	1.53 ± 0.03	348.88 ± 17.35	106/81	0.85 ± 0.02	
8 (F)	1.48 ± 0.04	345.00 ± 15.00	111/89	0.84 ± 0.04	
8 (M)	1.41 ± 0.08	386.25 ± 11.17	119/96	0.84 ± 0.03	
Group 2 (2 to 7 mg/dl)					
10 (P)	5.96 ± 0.26	$298.00 \pm 9.63^*$	101/71	0.76 ± 0.06	
14 (F)	5.18 ± 0.27	$292.85 \pm 10.60*$	98/72	0.79 ± 0.03	
3 (M)	4.86 ± 0.46	$306.66 \pm 14.53^*$	105/68	0.85 ± 0.07	
Group 3 (7 to 11 mg/dl)					
6 (P)	8.15 ± 0.22	303.33 ± 17.44	82/55*	0.73 ± 0.06	
3 (F)	7.87 ± 0.54	$273.33 \pm 6.66^*$	90/57	$0.66 \pm 0.01^{\circ}$	
6 (M)	9.63 ± 0.49	$293.33 \pm 8.43^*$	104/70	$0.77 \pm 0.03^{\circ}$	
Group 4 (>11 mg/dl)					
5 (P)	15.76 ± 1.57	$284.00 \pm 13.26^*$	68/40*	$0.36 \pm 0.13^{\circ}$	
7 (F)	13.26 ± 0.65	$261.42 \pm 9.86^*$	92/60*	$0.47 \pm 0.05^{\circ}$	
8 (M)	13.59 ± 0.81	$282.85 \pm 14.75^*$	104/74	$0.57 \pm 0.10^{\circ}$	

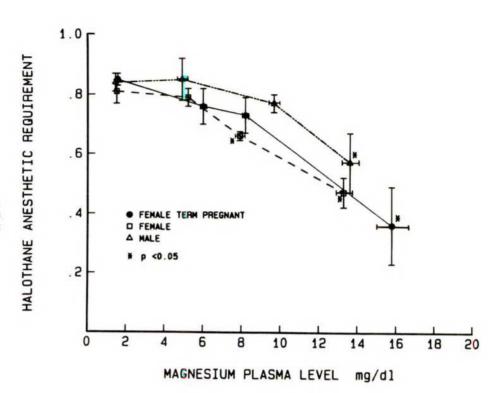
P, F, and M refer to pregnant, female, and male rats, respectively. Means \pm sem shown. *Statistical significance (P < 0.05) shown for anesthetic request.

olar concentrations of halothane were measured using gas liquid chromatography. MAC was established using a tail-clamp technique and was considered to be the point midway between the highest concentration of halothane that produced a positive response (somatic motion) and the lowest concentration of halothane that produced a negative response. MgSO₄ was administered by slow continuous infusion to 25 rats (8 male, 8 female, and 9 at term pregnancy) using infusion rates of approximately 3.5, 5.0, and 7.0 mg·kg⁻¹·min⁻¹ for at least 30 minutes before MAC was redetermined. With each MAC determination, arterial blood gas tensions (Corning 178), plasma Mg++ (Technicon RA 1000) and CA++ (Nova 2) levels, heart rate (HR), blood pressure (BP), and temperature (T) were measured. Ritodrine hydrochloride was infused in nine rats (five female, four male) at doses of 10 and 100 μ g·kg⁻¹·min⁻¹. The 5 female rats received 2 days of ritodrine pretreatment of 1 mg/kg subcutaneously twice a day. MAC was redetermined after 30 minutes of each infusion and plasma glucose levels, arterial blood gas tensions, HR, BP, and T were measured. Means and SEM were determined and statistical significance was established using an analysis of variance. A P value of 0.05 was considered statistically significant.

Results

The intravenous infusion of magnesium sulfate using the rates described results in plasma Mg⁺⁺ levels that were divided into four groups. Group 1 (control) with Mg⁺⁺ levels of <2 mg/dl, group 2 with Mg⁺⁺ levels between 2-7 mg/dl, group 3 with Mg++ between 7-11 mg/dl, and group 4 with Mg⁺⁺ levels above 11 mg/dl. MAC reduction, Mg++ levels, and the measured physiologic parameters for each group are shown in Table 1. Magnesium produced a reduction in halothane MAC that was nonlinearly dependent on plasma Mg++ levels (Fig. 1). The anesthetic requirement in male, female, and term pregnant control rats were not different from one another. With magnesium plasma levels of 7-11 mg/dl, an approximately 20% MAC reduction occurred in the female and term pregnant rats. When plasma levels were >11 mg/dl (group 4), a further decrease in anesthetic requirement, an approximately 40-60% MAC reduction, occurred in the female and pregnant groups. The anesthetic requirement in group 4 for all rats was significantly less than in groups 1, 2, and 3. Group 3 female and term pregnant female rats had a significantly lower MAC than did control rats. The male rats in group 3 were not significantly different from those in groups 1 and 2.

Arterial blood gas tensions, pH, and ionized Ca⁺⁺ levels remained within physiologic range. Although depression of HR and BP was evident at higher Mg⁺⁺ levels, tissue perfusion was maintained as evidenced by lack of development of metabolic acidosis. The absence of neuromuscular blockade was documented by discontinuing halothane and allowing spontaneous movement to resume while continuing the MgSO₄ infusion at 7.0 mg·kg⁻¹·min⁻¹.



<u>Figure 1</u>. Halothane requirement as a function of Mg⁺⁺ plasma levels in rats (male and pregnant and nonpregnant female).

Table 2. Anesthetic and Physiologic Effects of Ritodrine

Ritodrine dose $(\mu g \cdot k g^{-1} \cdot min^{-1})$	MAC reduction (%)	Heart rate (beats/min)	Blood pressure (mm Hg)	рН	Paco ₂ (mm Hg)
Control $(n = 9)$	0 ± 0	363 ± 13	127/99	7.46 ± 0.03	38 ± 4
10 (n = 9)	1.55 ± 1.2	409 ± 11	121/86	7.43 ± 0.01	38 ± 1
$100 \ (n = 9)$	2.66 ± 1.5	478 ± 10	108/72	7.36 ± 0.01	45 ± 2

The infusion rates of ritodrine employed in this study (from 2 to 50 times greater than those used clinically in humans) produced no significant change in anesthetic requirement. Subcutaneous pretreatment with ritodrine was likewise without effect. Significant tachycardia was noted in all rats during ritodrine infusion. Blood pressure, metabolic parameters, and temperature remained essentially unchanged from control values (Table 2).

Discussion

Parturients with toxemia of pregnancy or those in premature labor receiving MgSO₄ therapy appear sedated. Reports in the literature from both animal (1,3) and human (2,4) studies have yielded conflicting reports as to the anesthetic effect of the magnesium cation. Early reports of "anesthesia" were later attributed to magnesium-induced cardiac depression and neuromuscular blockade, with resultant muscle

weakness, hypoxia, and hypercarbia diminishing the response to noxious stimuli. In the present study, these factors were noncontributory. Mechanical ventilation with halothane in oxygen prevented hypercarbia and hypoxia. All rats moved actively after discontinuing halothane despite continuing MgSO₄ administration, effectively ruling out significant muscle weakness interfering with MAC determination. Monitored metabolic parameters and temperature remained physiologic, reflecting adequate tissue perfusion.

Plasma Mg⁺⁺ levels achieved in our rats correlate with levels achieved clinically. The higher levels may be seen in severely toxemic parturients with concomitant renal insufficiency and impaired excretion of magnesium. Current practice is to monitor plasma Mg⁺⁺ levels when MgSO₄ is administered in the clinical setting. In general, levels of 4 mg/dl prevent seizures; levels of 10–12 mg/dl are associated with loss of deep tendon reflexes (knee jerk); respiratory depression occurs at levels of 12–15 mg/dl; and at

levels above 15 mg/dl, complete heart block and cardiac arrest may occur (7). When Mg⁺⁺ levels are not monitored, clinicians try to avoid levels of 12 mg/dl by discontinuing MgSO₄ administration when deep tendon reflexes are obtunded.

Magnesium sulfate therapy affects many aspects of the anesthetic management of toxemic parturients. The potentiating interaction between neuromuscular blocking agents and magnesium has been well described (8). Respiratory function and ventilatory reserve are compromised at higher Mg++ levels without concomitant relaxant administration. Cardiac depression and vasodilation may result in hypotension. The present data document a significant aresthetic effect of magnesium. At clinical levels of 7-11 mg/dl, an approximately 20% decrease in anesthetic requirement was observed in female and term pregnant rats. When plasma magnesium levels increased further, a marked anesthetic effect, up to 60% MAC reduction, occurred. These studies suggest that monitoring the plasma Mg++ levels optimizes the care of the often complicated, physiologically compromised toxemic patient.

Drugs that alter CNS monoamine levels effect anesthetic requirements. Cocaine and amphetamine acutely increase postsynaptic norepinephrine levels (9) and also increase anesthetic requirements (5). Methyldopa and reserpine deplete CNS monoamines and decrease MAC (5). Ritodrine hydrochloride, a synthetic monoamine with principally β -2 activity, has tocolytic properties. Although it is unknown if ritodrine crosses the blood-brain barrier, it is reported to cause CNS stimulation, restlessness, and anxiety when it is administered to parturients in premature labor (10). This study reveals no change in anesthetic requirements, despite ritodrine infusion rates up to $100~\mu g \cdot k g^{-1} \cdot min^{-1}$ (human dose range of $2-5~\mu g \cdot k g^{-1} \cdot min^{-1}$ (9).

Magnesium sulfate and ritodrine are effective to-

colytic agents in current clinical use. Interactions between ritodrine and anesthetic agents have not been described, and this study demonstrates no effect of ritodrine on anesthetic requirements. In marked contrast, MgSO₄ affects many aspects of physiology relevant to the anesthesiologist. The present demonstration of acutely decreased anesthetic requirements with MgSO₄ administration further supports the practice of monitoring serum Mg levels and mandates careful titration of all anesthetic agents to avoid overdosing high risk patients requiring MgSO₄.

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Effect of Naloxone Infusion on Analgesia and Respiratory Depression after Epidural Fentanyl

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GUENERON JP, ECOFFEY CI, CARLI P, BENHAMOU D, GROSS JB. Effect of naloxone infusion on analgesia and respiratory depression after epidural fentanyl. Anesth Analg 1988;67:35–8.

The efficacy of two dosage regimens of intravenous naloxone were compared to avoid nonrespiratory side effects and respiratory depression and yet to preserve analgesia (maximum tolerance to periostal pressure over the tibia) after administration of 200 µg epidural fentanyl. Three groups of eight patients were studied: group I patients received a loading dose of 0.4 mg IV naloxone followed by naloxone infusion at a rate of 10 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Group II patients received a loading dose of 0.2 µg naloxone followed by a naloxone infusion at a rate of 5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Group III patients received a saline infusion at a rate of 20 ml/hr. Epidural fentanyl significantly increased tolerance to periostial pain in all three groups (respectively, $+38 \pm 20\%$, $+36 \pm 16\%$, and $+35 \pm 14\%$) (mean \pm sp; P < 0.05). The naloxone infusion significantly reduced this effect in groups I and II, respectively, $-40 \pm 20\%$ and $-37 \pm 28\%$

below prenaloxone levels) (P < 0.05). Nonrespiratory side effects were also reversed in groups I and II. In group III, neither periostial analgesia nor nonrespiratory side effects were affected. The baseline slopes of VE/Pet_{CO} , were 2.34 \pm 1.01, 2.14 \pm 0.66, and 2.68 \pm 1.14 L·min⁻¹·mm Hg⁻¹, respectively, in groups I, II, and III. Epidural fentanyl significantly decreased the slope below baseline levels in each group: $-21 \pm 16\%$, $-22 \pm 17\%$, and -19± 32%, respectively, in groups I, II, and III. Thirty minutes after the start of naloxone infusion the slope of $\dot{V}E/P_{ET_{CO}}$ increased significantly in group I (+22 ± 14%) from prenaloxone value) (P < 0.05), decreased significantly in group III ($-11 \pm 17\%$ from prenaloxone value) (P <0.05), and remained unchanged in group II (+10 \pm 25% from prenaloxone value). Although high-dose naloxone reverses the respiratory depression associated with epidural fentanyl administration, there is a concomitant decrease in the quality of analgesia.

Key Words: PAIN—postoperative. ANALGESICS—fentanyl. ANTAGONISTS, NARCOTICS—naloxone. ANESTHETIC TECHNIQUES—epidural.

Epidural fentanyl has been advocated for postoperative pain relief (1). However, epidural fentanyl also induces respiratory depression as documented by a decrease in the ventilatory response to CO_2 (2,3). The respiratory depression induced by epidural morphine can easily be reversed by naloxone (4,5). Respiratory depression after epidural buprenophine, however, has been reported to be resistant to naloxone, possibly because of the high affinity of this opioid for opiate receptor (6). No data are available on the efficiency of naloxone in reversal of respiratory depression induced

by epidural fentanyl. The aim of this study was to determine the effects of two dosage regimens of naloxone on analgesia and ventilatory response to CO₂ after the epidural injection of fentanyl.

Methods

Patients

We studied 24 patients ranging in age from 19 to 47 years who were scheduled for lithotripsy; they were unpremedicated and had fasted overnight. The study protocol received institutional approval, and we obtained informed consent from all patients. We randomly assigned patients to one of the three study groups (eight patients each).

Procedure for Epidural Injection

We began an infusion of Ringer's lactate solution (3 ml \cdot kg⁻¹ \cdot h⁻¹) through a venous catheter. The ECG

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was continuously displayed on an electrocardioscope and arterial blood pressure was measured by a sphygmomanometer cuff. An epidural catheter was inserted at the L3-L4 interspace after which the patients remained supine in the 45° head-up position. After the first set of measurements (baseline), we injected 200 µg fentanyl in 10 ml saline through the epidural catheter. Thirty minutes later a second set of measurements was performed. Patients in group I were then given a loading dose of 0.4 mg naloxone IV followed by a continuous IV naloxone infusion at a rate of 10 μ g · kg⁻¹ · hr⁻¹; group II patients received a loading dose of 0.2 mg naloxone IV followed by continuous IV naloxone infusion at a rate of 5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Group III patients had a continuous infusion of normal saline at a rate of 20 ml/hr. Thirty minutes after the start of naloxone or saline infusion, a third set of measurements was performed. At the end of the study, after an aspiration test, we injected 3 ml 2% lidocaine with epinephrine 1:200,000 to detect possible accidental intravascular or intradural injection. Local anesthetics solution was then injected through the epidural catheter to provide operative analgesia.

Clinical Effects

We evaluated analgesia before and 30 minutes after fentanyl injection as well as 30 minutes after naloxone infusion. We used a spring-loaded rod to determine the maximum tolerable periostial pressure over the distal and of the tibia (7); we performed each triplicate determination and averaged the results. We also recorded adverse effects such as pruritis, nausea, and drowsiness.

Ventilatory Measurements

Respiratory rate (RR) and minute-ventilation ($\dot{V}E$) were recorded with the subjects breathing room air and during CO_2 rebreathing tests with a mouthpiece and a nose-clip, through a pneumotachograph (Fleisch no. 2) and a Rudolph nonrebreathing valve. Instrument dead space was 70 ml. Resistances to inspiratory and expiratory flows were 2.4 and 3.6 cm $H_2O \cdot \sec^{-1} \cdot L^{-1}$ respectively, at a flow of 1 L/sec. Ventilatory response to CO_2 was assessed by rebreathing for 4 to 5 minutes from a 7-liter spirometer filled with a mixture of 7% CO_2 in O_2 . Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven-Holland) connected to the pneumotachograph, previously calibrated with a 1-

<u>Table 1</u>. Percentage Change from Baseline Values and from Prenaloxone Value in Tolerance to Periostial Pressure.

	Fentanyl	Naloxone or saline
Group I	38 ± 20*	$-40 \pm 20 \dagger$
Group II	$36 \pm 16^*$	$-37 \pm 28 t$
Group III	$35 \pm 14^*$	+6 ± 21*†

Mean values ± sp.

liter syringe of air. End-tidal CO₂ tension (Pet_{co2}) was measured with a Godart capnograph (Bilthoven-Holland) calibrated with 5%, 7%, and 9% mixtures of CO₂ in O₂, verified to be within 1% using Scholander microanalysis. Pneumotachograph and capnograph outputs were interfaced to a CBM SX64 computer with an analog-to-digital converter (8). After converting ventilatory variables to BTPS, linear regression equations were computed from VE and Pet_{co2} for each CO₂ challenge curve. The correlation coefficients ranged from 0.94 to 0.98.

Statistical Analysis

All the values are expressed as mean \pm sp. The statistical significance of differences between the three groups in age and weight was evaluated using the nonparametic Mann-Whitney test. The significance of differences in ventilatory measurements between the three groups was evaluated with the use of two-way ANOVA. The significance of differences between respiratory measurements at each time interval and control values was tested using an ANOVA followed by a *t*-test. Values of P < 0.05 were considered statistically significant.

Results

Age, weight, and baseline slope $\dot{V}E/Pet_{co_2}$ slopes were similar in the three groups.

Clinical Results

Periostial pain thresholds increased significantly in all three groups 30 minutes after epidural fentanyl, and decreased significantly after naloxone infusion in groups I and II, whereas periostial pain threshold increased further in group III (Table 1). Thirty minutes after the fentanyl injection, five patients in group II, six patients in group III, and six patients in group III

^{*}P < 0.05 v control value; †P < 0.05 v prenaloxone value.

Table 2. Resting Respiratory Variables before, 30 Minutes after Epidural Fentanyl, and 30 Minutes after the IV Infusion of Naloxone or Saline

	Control	Fentanyl	Saline or naloxone
Resting Petco,			
Group I	35 ± 2	37 ± 3	37 ± 2
Group II	35 ± 2	37 ± 5	35 ± 5
Group III	34 ± 2	37 ± 3	37 ± 3
Resting RR (breaths/min)			
Group I	15 ± 3	16 ± 3	16 ± 5
Group II	14 ± 5	13 ± 4	15 ± 3
Group III	14 ± 2	15 ± 2	14 ± 2
Resting VE (1/min)			
GROUP I	9.3 ± 3.1	8.8 ± 2.9	9.5 ± 2.8
GROUP II	8.6 ± 2.9	7.7 ± 3.2	9.1 ± 3.6
GROUP III	9.5 ± 1.3	8.7 ± 1.5	8.7 ± 1.2

Mean values \pm sem. Abbreviations: PET_{co2}, end-tidal CO₂ tension; RR, respiratory rate; $\dot{V}E$, minute-ventilation.

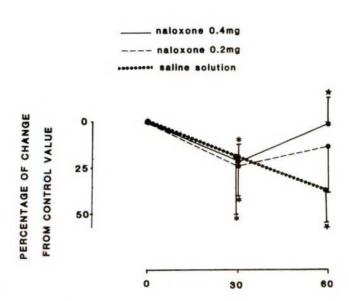
felt drowsy; three patients in group I, four patients in group II, and five patients in group III had pruritis; two patients in group II had nausea. These side effects completely disappeared after naloxone infusion in patients in group I and II, but persisted in group III patients.

Ventilatory Measurements

Resting ventilatory variables did not change in any of the groups during the study (Table 2). Baseline $\dot{\rm VE/Pet_{Co_2}}$ slopes were 2.34 \pm 1.01, 2.14 \pm 0.66, and 2.68 \pm 1.14 min · L⁻¹ · mm Hg⁻¹, respectively, in groups I, II, and III. The slope of $\dot{\rm VE/Pet_{Co_2}}$ decreases significantly 30 minutes after the epidural fentanyl injection in all three groups (Fig. 1). Thirty minutes after the start of naloxone or saline infusion, the slope of $\dot{\rm VE/Pet_{Co_2}}$ increased significantly in group I, decreased in group III, and remained unchanged in group II.

Discussion

We found that the analgesia as well as the respiratory and nonrespiratory side effects induced by 200 μ g epidural fentanyl were reversed by the high dose of naloxone. The low dose of naloxone reversed the analgesia and nonrespiratory side effects but not the respiratory depression. In addition, the study confirms that respiratory depression may occur in <30 minutes after the epidural administration of liposoluble opioid such as fentanyl (2,3), a response also seen with alfentanil (9).



<u>Figure 1</u>. Percentage change from baseline values in the slope of $\overline{\text{VE/Pet}}_{\text{co}_2}$ 30 minutes after administration of fentanyl and 30 minutes after naloxone or saline infusion. Mean Values \pm sp. * P < 0.05 vs control value. $\bigstar P < 0.05$ vs prenaloxone value.

Side effects such as drowsiness, pruritis, and nausea were reversed with both naloxone infusion doses, as reported with epidural morphine (4,5). On the other hand, intermittent IM injection of 0.4 naloxone (4) and continuous IV infusion of naloxone (5) has been reported to reverse respiratory depression after epidural morphine. In the present study, a high infusion dose of naloxone was necessary to reverse respiratory depression after the epidural injection of the liposoluble opioid, fentanyl. In contrast to the present finding, a low infusion rate of naloxone can reverse the respiratory depression associated with epidural morphine. The differences in response to naloxone with epidural morphine and fentanyl may be related to the difference in lipid solubilities of morphine and fentanyl. Also, in our study we used a more sensitive assessment of the control of the ventilation, ventilatory response to CO2, whereas Rawal et al. used the measurements of resting Paco, in patients with postoperative pain (5). Low infusion doses of naloxone also decrease analgesia less than do high infusion doses (5). The graded response in the reversal by naloxone of the suppression of noxiously evoked activity of neurons due to spinal morphine administration has been previously reported in animals (10). However, after epidural fentanyl injection in our study, both naloxone infusion doses equally reversed the analgesia. This is not surprising for two reasons: we studied only the maximum tolerance to periostial pressure rather than graded stimuli. Second, the absence of a dose-response relation in the

reversal by naloxone of the suppression of noxiously evoked activity of neurons due to spinal fentanyl administration has been reported in animals (11).

In conclusion, low dose intravenous infusion of naloxone is inadequate to reverse the respiratory depression after epidural fentanyl. However, high dose intravenous infusion of naloxone necessary to prevent respiratory depression after epidural fentanyl significantly decreases the quality of analgesia. This study demonstrates that it is difficult to reverse the respiratory depression of epidural liposoluble narcotics selectively without also decreasing the analgesic effect.

We thank Mrs. Janet Miller and Miss Guylaine Rosine for secretarial assistance.

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Rapid Administration of a Narcotic and Neuromuscular Blocker:

A Hemodynamic Comparison of Fentanyl, Sufentanil, Pancuronium, and Vecuronium

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GRAVLEE GP, RAMSEY FM, ROY RC, ANGERT KC, ROGERS AT, PAUCA AL. Rapid administration of a narcotic and neuromuscular blocker: a hemodynamic comparison of fentanyl, sufentanil, pancuronium, and vecuronium. Anesth Analg 1988;67:39–47.

High-dose narcotic anesthetic inductions usually avoid circulatory depression better than do other techniques; however, the selection of a narcotic and neuromuscular blocker influences subsequent hemodynamic responses. One hundred-one patients having aortocoronary bypass graft (CABG) surgery were investigated using four combinations of a narcotic and neuromuscular blocker: group FP (fentanyl 50 µg/kg, pancuronium 100 µg/kg); group FV (fentanyl 50 µg/kg, vecuronium 80 µg/kg); group SP (sufentanil 10 µg/kg, pancuronium 100 µg/kg); and group SV (sufentanil 10 µg/kg, vecuronium 80 µg/kg), each combination being administered over 2 minutes. Hemodynamic functions were then monitored for 10 minutes before tracheal intubation. Significant changes included increases in heart rate in the groups receiving pancuronium and decreases in those receiving vecuronium. In all groups mean arterial pressure initially decreased; systemic vascular resistance index decreased significantly in all groups except SV. Cardiac index decreased significantly only in group SV. Circulatory depression requiring treatment with vasopressor or anticholinergic drugs was more common in patients given vecuronium. Cardiac arrhythmia occurred most often in group SP; only in group FP were there no arrhythmias, ischemic changes, or hemodynamic disturbances requiring intervention. Time to onset of neuromuscular blockade did not differ among the four groups, but transient chest wall rigidity occurred significantly more often with sufentanil than with fentanyl. Overall, the fentanyl/pancuronium combination afforded the greatest hemodynamic stability, whereas the sufentanil/vecuronium combination proved least satisfactory because of bradycardia and hypotension, requiring treatment in 35% of group SV patients. Differences in anesthetic premedication, social habits, preoperative medications, narcotic and muscle relaxant doses, and speed of anesthetic drug administration may also influence hemodynamic responses and may explain differing results reported by others using the same drug combinations.

Key Words: ANESTHETICS, INTRAVENOUS fentanyl, sufentanil. NEUROMUSCULAR RELAXANTS—pancuronium, vecuronium.

High-dose narcotic induction of anesthesia, defined as the intravenous administration of a dose exceeding $25 \mu g/kg$ of fentanyl (or an equipotent dose of another narcotic) before tracheal intubation has gained widespread popularity for patients undergoing coronary artery bypass graft (CABG) surgery. This technique's

reports from Stanley et al. paired fentanyl with succinylcholine (1,2), current clinical practice frequently couples fentanyl with pancuronium (4–10). Some authors report minimally altered hemodynamics following that combination (4,5), whereas others report increases in heart rate or arterial pressure (6–9). Thomson and Putnins (10) warn that the fentanyl/pancuronium combination may produce tachycardia and myocardial ischemia. Sufentanil, a more potent

fentanyl congener, offers a more rapid onset of action

and earlier wake-up time than does fentanyl (11,12).

popularity derives from its usual association with a

stable hemodynamic course (1–3). Although the early

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Although some hail its virtues (4,13), others associate sufentanil with troublesome changes in heart rate or blood pressure (14–17). Vecuronium, a nondepolarizing neuromuscular blocker of intermediate duration of action, is said to have few direct hemodynamic effects (18–20), though some have reported bradycardia during its use with a narcotic (17,21–30). Because different study methods make comparisons difficult, we decided to examine prospectively four induction techniques utilizing each of four possible narcotic/relaxant combinations of fentanyl, sufentanil, pancuronium, and vecuronium.

Methods

After receiving approval from our human studies committee, informed consent was obtained from 101 patients scheduled for elective coronary artery bypass graft (CABG). Exclusion criteria included left main coronary artery obstruction, ejection fraction < 0.40, myocardial infarction within 7 days, the clinical impression that airway maintenance with a mask would be difficult, and preoperative use of continuous intravenous infusions containing vasoactive or antiarrhythmic drugs. All cardiac and antihypertensive medications were administered on the day of surgery. Each patient was premedicated with oral lorazepam 50 μg/kg and intramuscular morphine 0.1 mg/kg, both drugs being administered 60-90 minutes before arrival in the operating room. Oxygen was administered by nasal cannula during placement of two peripheral intravenous catheters, a radial or brachial artery catheter, and a 7.5F American Edwards VIP pulmonary artery (PA) catheter. Using an even-odd day and alternating-week method, patients were randomly assigned to one of four anesthetic induction techniques: 1) group FP, fentany 50 μ g/kg and pancuronium 100 μ g/kg (26 patients); 2) group FV, fentanyl 50 µg/kg and vecuronium 80 μ g/kg (22 patients); 3) group SP, sufentanil 10 μ g/kg and pancuronium 100 μg/kg (30 patients); or 4) group SV, sufentanil 10 μ g/kg and vecuronium 80 μ g/kg (23 patients). In each group, 100% oxygen was delivered by facemask for 5 minutes before the narcotic and relaxant were infused simultaneously over 2 minutes through the side-port of the PA catheter introducer. Positive pressure ventilation by mask was initiated when the patient lost consciousness, maintaining end-tidal CO₂ between 30 and 37 mm Hg as measured by mass spectrography.

Hemodynamic measurements were made during oxygen administration, 2, 5, and 10 minutes after completion of the anesthetic infusions, and 2 minutes

after tracheal intubation. In all instances, the 2-minute postinfusion hemodynamic measurements were completed before administration of any vasoactive, β -adrenergic blocking, or anticholinergic drug. After these measurements, each anesthesiologist selected his or her own criteria for hemodynamic intervention. The most frequent interventions were phenylephrine or ephedrine for mean arterial pressures <65 mm Hg, atropine for heart rates <45 beats/min, nitroglycerin for ST segment changes or mean arterial pressures >95 mm Hg, and propranolol for heart rates >90 beats/min. Laryngoscopy and tracheal intubation were accomplished after completing the 10-minute postinfusion hemodynamic measurements.

The measurements included heart rate (HR), arterial pressures, pulmonary arterial pressures, pulmonary capillary wedge pressure (PCW), right atrial pressure (CVP), and duplicate iced thermodilution cardiac outputs (American Edwards CO-Set and 9520A Cardiac Output Computer). When the two cardiac output measurements differed by more than 10%, additional measurements were taken until two consecutive outputs differed less than 10% (a maximum of four determinations). The following hemodynamic parameters were derived using standard formulas: cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI), pulmonary vascular resistance index (PVRI), and systemic vascular resistance index (SVRI). Arterial pressures were measured via Gould 60-cm high-pressure tubing, a Gould P23b strain gauge, Hewlett-Packard 8805D pressure amplifier, and a Midwest Analog and Digital Video Information System. Pulmonary artery and CVP measurement systems differed from the above only by the use of a 15-cm (rather than 60-cm) segment of Gould high-pressure tubing. Each strain gauge was zero-balanced and mercury-calibrated before use. Dynamic response evaluation of the arterial pressure monitoring system showed natural frequency >20 Hz and damping coefficients of 0.25 to 0.30.

Electrocardiogram leads II and V_5 were continuously monitored using a diagnostic quality (0.05–100 Hz) Hewlett-Packard (HP)8811A ECG amplifier and 78309A oscilloscope. Signal amplitude was standardized to 10 mm/mV. Electrocardiographic rhythm and ST segment status were observed with each set of hemodynamic measurements, any questionable diagnoses being recorded on a tracing with an HP 7754A recorder at a 25 min/sec paper speed.

After alcohol skin preparation over the distal forearm, two skin electrodes were placed parallel to the course of the ulnar nerve and cable-connected to a MiniStim (Professional Instruments Company) nerve stimulator. Upon completing the anesthetic infusion, a train-of-four supramaximal twitch stimulus was applied every 30 seconds, recording the onset time for maximal twitch suppression. Chest wall rigidity was subjectively assessed using a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). These categories were defined as follows: 1) mild rigidity: positive pressure ventilation by mask was slightly difficult before the onset of neuromuscular blockade; 2) moderate rigidity: mask positive pressure ventilation was difficult, but could be accomplished with high peak airway pressures; 3) severe rigidity: mask ventilation was inadequate until the onset of neuromuscular blockade. Upper airway obstruction was carefully assessed and treated, and thus eliminated as a cause of ventilatory difficulty.

Two-by-two analysis of variance (general linear models) was used to statistically compare demographic characteristics by group. Characteristics compared among the groups included sex, age, height, weight, number of distal grafts, previous myocardial infarction (MI), ejection fraction (EF), left ventricular end-diastolic pressure (LVEDP), and preoperative medications (nitrates, β -adrenergic blockers, nifedipine, diltiazem, verapamil, diuretics, and digoxin). The same method helped assess the influence of preoperative cardiac medications on the hemodynamic changes observed after induction of anesthesia. Hemodynamic measurements and the onset of maximal twitch suppression were compared using repeated two-tailed t-tests with a modified Bonferroni correction for multiple testing. Chest wall rigidity scores were compared between groups by logit analysis. The specific influence of the two narcotics and the two relaxants on the observed hemodynamic changes was evaluated by two-by-two factorial analysis of variance. Two-by-two logit analysis was used to compare the frequency of intervention with vasoactive drugs as a function of the narcotic or muscle relaxant. The χ^2 method compared the incidence of ECG rhythm disturbances between groups.

Results

Demographics for the four groups fell within the following ranges: male sex, (65-82%); age, $53(\pm10)-61(\pm8)$ years; height, $173(\pm10)-175(\pm12)$ cm; weight, $76(\pm14)-81(\pm11)$ kg; distal grafts, $2.5(\pm1.0)-3.5(\pm0.5)$; previous MI, 43-74%; EF, $0.58(\pm0.09)-0.64(\pm0.11)$; LVEDP, $14(\pm4)-16(\pm5)$ mm Hg. Among the medications used in over 20% of patients in any group, utilization (percentage of pa-

tients in group) ranges were as follows: nitrates 68–93%, β -adrenergic blockers 65–77%, nifedipine 42–64%, diltiazem 5–30%, and diuretic 9–20%. A greater number of distal grafts were placed in patients receiving pancuronium than in those receiving vecuronium (P < 0.05). No other demographic differences reached statistical significance.

Figure 1 shows the hemodynamics over time by group. All groups had similar hemodynamics in the control period. After anesthetic induction, heart rate increased in groups given pancuronium, but decreased in groups receiving vecuronium. Mean arterial pressure (MAP) decreased significantly 2 minutes after infusion in all groups, and remained significantly below control values in group SP. Systolic and diastolic arterial pressures decreased in parallel. Cardiac index decreased significantly in group SV. All groups had initial reductions in SVRI (significant in groups FP, SP, and SV); only in group SP was this change sustained. CVP increased in group FP after induction, representing the only significant change in right- or left-sided filling pressures in any of the groups.

Pharmacologic interventions to improve unsatisfactory hemodynamics were made in 21 patients (0 in group FP, 8 (36%) in group FV, 5 (17%) in group SP, 8 (35%) in group SV). All but two interventions (both in group FV) were made immediately after the 2 minute postinfusion measurements. Sixteen of 21 interventions consisted of a vasopressor or atropine (or both), and the remaining 5 interventions (2 in group FV, 3 in group SP) consisted of a vasodilator or β-adrenergic blocker (or both). Groups FP, SP, and SV each had one patient with a transient MAP <65 mm Hg that was not treated with a vasopressor. Two patients in group SV and one in group FV had heart rates <45 beats/min unaccompanied by hypotension or an increase in PA or PCW pressures; these patients were not treated for bradycardia. Patients given vecuronium required early (2 min postinfusion) interventions more often than did patients receiving pancuronium (P < 0.01). Recognizing that vasoactive drug interventions influenced some patients' subsequent hemodynamic measurements, the hemodynamic analysis was repeated after excluding those who received any vasoactive drug during the study. This did not alter the direction or the statistical significance of the changes shown in Figure 1.

Of the 101 patients studied, 3 had ST segment depression >0.1 mV in lead II or V5 before anesthetic induction. During the study period, seven additional patients developed ST segment changes (none in group FP, two in group FV, four in group SP, one in group SV). These changes were distributed evenly

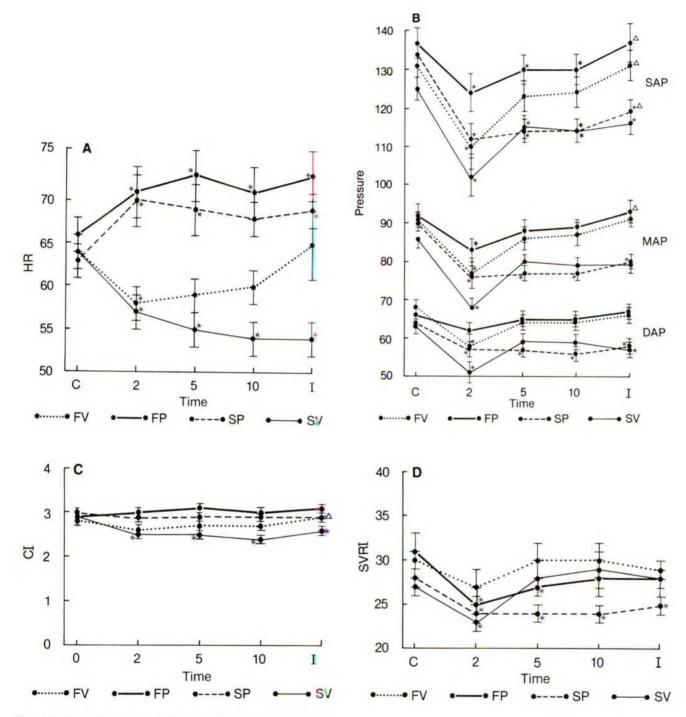
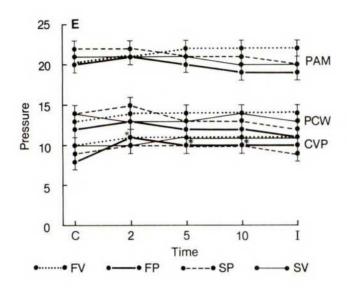
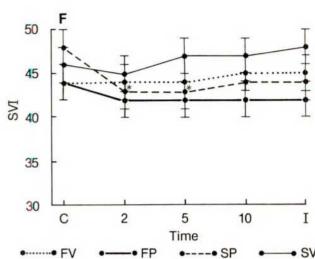
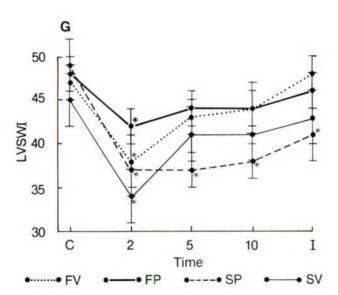


Figure 1. Hemodynamic variables as a function of time. Group abbreviations are listed in Methods. Times: C, control; 2,5, and 10,2,5, and 10 minutes after completing drug infusions, respectively; 1–2 minutes after tracheal intubation. (A) Heart rate (HR, beats/min); (B) Arterial pressures (mm Hg); systolic (SAP); mean (MAP), diastolic (DAP); (C) cardiac index (CI, L · min · m²); (D) systemic vascular resistance index (SVRI), mm HG |x| min |x| m²-L); (E) pulmonary arterial mean (PAM), pulmonary capillary wedge (PCW), and right atrial (CVP) pressures (mm Hg); (F) stroke volume index (SVI, ml/m²); (G) left ventricular stroke work index (LVSWI, gm-m/m²); (H) pulmonary vascular resistance index (mm Hg |x| min |x| m²/L). *P < 0.05 compared with control; $^{\Delta}P$ < 0.05 compared with 10 minutes after infusion.







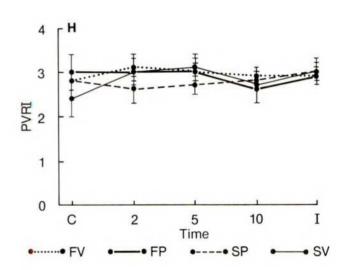


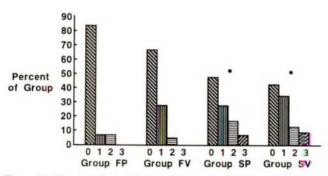
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across the measurement periods. During the control measurements, one patient had premature ventricular contractions (PVCs). Nine additional patients developed arrhythmias during the study. Six of those arrhythmias occurred in group SP (P < 0.05 compared with group FP): three patients developed AV junctional rhythm, two had PVCs, and one had premature atrial contractions. Two patients in group FV (not significant compared with group FP) and one patient in group SV experienced PVCs; no rhythm disturbances occurred in group FP.

Time to development of maximum twitch suppression ranged from 1 to 11 minutes (mean of 3.5 ± 0.2 [se] minutes). Onset time for neuromuscular block-

ade did not differ among the study groups. Figure 2 shows the frequency distribution for chest wall rigidity. Patients given sufentanil had higher rigidity scores (P < 0.05) than patients receiving fentanyl, but the selection of neuromuscular blocking drug did not influence chest wall rigidity.

Pooling the entire study population, in patients receiving preoperative β -adrenergic blockers, heart rates increased significantly less between control and postintubation periods than they did in patients without β -adrenergic blockade (P < 0.01). Aside from this observation, the presence or absence of β -blockers or calcium channel blockers did not influence changes observed in heart rate, mean arterial



<u>Figure 2</u>. Chest wall rigidity scores expressed as a percentage of patients in each group: 0, no rigidity; 1, mild rigidity; 2, moderate rigidity; 3, severe rigidity. *Sufentanil groups experienced rigidity significantly more frequently than did fentanyl groups (P < 0.05).

pressure, cardiac index, or stroke volume index. All β -blockers were pooled for this analysis, whereas calcium channel blockers were considered both individually and collectively.

Discussion

All four rapid induction techniques caused some reduction in blood pressure (BP) and SVRI. Only patients receiving the SP combination sustained significant reductions in BP and SVRI throughout the study period. Two previous studies also found reductions in BP and systemic vascular resistance using the sufentanil/pancuronium combination (14,15). Depending on the study, one could conclude that the fentanyl/pancuronium combination increases, decreases, or does not change BP or systemic vascular resistance (SVR) (4–9,31). The most common observation has been that this drug combination causes a modest decrease in BP and SVR, sometimes failing to reach statistical significance, before intubation and surgical incision.

Combining either narcotic with pancuronium increased heart rate in the present study, whereas combining these narcotics with vecuronium decreased heart rate. Several other groups have also reported an increase in heart rate when combining pancuronium with fentanyl or sufentanil (6-9,15,16, 21,31). Using fentanyl alone or combining it with succinylcholine generally decreases heart rate, owing to a centrally mediated vagotonic effect of fentanvl (1-3). Pancuronium offsets this effect with its peripheral vagolytic and sympathomimetic effects (20). Thomson and Putnins (10) observed myocardial ischemia during induction of anesthesia in 3 of 12 patients given the FP combination, the increase in HR after FP (from 58 to 76 beats/min) being greater than what we observed (from 66 to 71 beats/min). While they administered fentanyl at $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ and

gave a bolus of pancuronium on loss of consciousness, possibly our simultaneous administration of fentanyl and pancuronium produced a more rapid increase in brain fentanyl concentration that more completely offset the vagolytic effect of pancuronium. Their use of scopolamine premedication represents another potentially important difference between the two studies, because scopolamine might augment the vagolytic effect of pancuronium.

We chose to inject the drugs over 2 minutes because we have observed that using this technique with fentanyl and pancuronium usually permits rapid airway control and loss of consciousness while avoiding chest wall rigidity. Equipotent narcotic and neuromuscular blocker doses were selected on the basis of previous investigations (14,19,32,33), with selection of neuromuscular blocking doses of 1.6 times the effective dose for 95% twitch suppression to hasten onset time (33). Reported sufentanil/fentanyl potency ratios vary from 5:1 to 10:1 (4,11,13,14, 32,34-39). Studies demonstrating comparable electroencephalographic changes (36,37) and surgical hemodynamic and humoral stress response suppression (38) support our selection of a 5:1 potency ratio. Determining narcotic potency ratios in human studies presents a formidable problem, however, because establishing a reliable indicator for high-dose narcotic anesthetic potency has proven elusive. Various markers such as loss of consciousness, electroencephalographic patterns, hemodynamic stability, total dose requirements, and endocrine changes have been used, but none of these can duplicate the reliability of minimal alveolar concentration (MAC) as a potency index for inhalation anesthesia.

Vecuronium lacks demonstrable autonomic effects in animal studies (40,41), and early human studies showed a negligible effect on heart rate (19,42). The investigations in humans were conducted during stable halothane or enflurane anesthesia. Use of vecuronium with a nitrous oxide and narcotic anesthetic technique tends to decrease heart rate, whereas pancuronium usually increases it (43,44). Several authors have reported asystole or marked bradycardia when using vecuronium with various doses of narcotics (17,22-25,29,30). The sufentanil/vecuronium combination appears particularly conducive to this (17,26,28). Salmenpera et al. (21) reported that vecuronium decreases heart rate if given after establishing stable high-dose fentanyl anesthesia. Gregoretti et al. administered vecuronium during enflurane and halothane anesthesia and observed a small decrease in heart rate in patients given enflurane (42). Narcotics can cause bradycardia via a central vagotonic effect (45), which vecuronium would not offset as

pancuronium does. If this explains our observations after vecuronium/narcotic combinations, we wonder why metocurine/narcotic combinations have not produced similar reports. It is possible that slight vaso-dilation from metocurine activates the baroreceptor reflex.

With the sufentanil/vecuronium combination, a significant reduction in cardiac index accompanied the decrease in arterial pressures despite unchanged cardiac filling pressures, which suggests that this combination depressed the myocardium. The reduction in heart rate may have contributed to this, but the decrease in heart rate after sufentanil/vecuronium should have produced a compensatory increase in SVI if myocardial contractility had not decreased (46). Directionally similar changes occurred in group FV, although the decrease in CI did not reach significance in that group. Changing from spontaneous to positive-pressure ventilation might have contributed to the decreased CI; however, this would not explain the uniqueness of the significantly decreased CI in group SV. The insignificant changes we found in PA, PCW, and CVP agree with previous investigations (1,3,5-9,14,15). The CVP increase in Group FP reached statistical but not clinical significance.

Pharmacologic interventions initiated after the 2-minute postinfusion hemodynamic measurements create some difficulty in analyzing data from subsequent time periods. It is likely that the vasopressor interventions influenced subsequent hemodynamics in group SV, and possibly did so in group FV. Although the numerical values change slightly if the patients receiving interventions are deleted, none of the statistically significant changes from the control period were altered by deletion of those patients. This held true for all postinfusion time periods. On the basis of these results, we elected to keep the four original randomized groups intact.

All four techniques adequately suppressed the hemodynamic response to laryngoscopy and intubation, presumably reflecting that well established property of high-dose narcotic inductions. After intubation, the increase in systolic arterial pressure in three of the four groups (FP, FV, SP) and in MAP in group FP were statistically but not clinically significant. Intubation also caused minor increases in heart rate that failed to reach statistical significance in any group. The observation that preoperative β -blocker therapy attenuated the increase above baseline levels in postintubation heart rate supports our clinical impression that adequate β -adrenergic blockade importantly complements anesthesia in patients undergoing CABG.

Our data suggest that the sufentanil/pancuronium

combination has the greatest propensity for ischemic ST segment changes and for arrhythmias, with the SP group accounting for four of seven ischemic ECGs and six of nine rhythm disturbances. When compared with the fentanyl/pancuronium group, only the incidence of rhythm disturbances reached statistical significance. Our 3% incidence of preinduction ischemia falls substantially below the 18% incidence recently reported by Slogoff and Keats (47). This difference may result from more restrictive exclusion criteria in the present study.

We caution against oversimplifying the clinical implications of our hemodynamic findings. As Heinonen and Yrjola (48) so eloquently wrote, "We realize that the hemodynamic effects of a neuromuscular blocking drug depend greatly on the milieu into which the drug is administered." The findings in our population of patients having CABG surgery may not apply to all patient populations. Additionally, slower drug administration might diminish the untoward hemodynamic responses so frequently observed in groups FV, SP, and SV. The faster anesthetic onset time for sufentanil may have contributed to the hemodynamic changes observed 2-minute postinfusion, because the onset of anesthesia diminishes sympathetic tone. However, this would not explain the occurrence of sustained changes in arterial pressures and SVRI in group SP and in cardiac index in group SV, while such changes did not occur in the fentanyl groups 5 and 10 minutes after completing the drug infusions. Ten minutes should prove sufficient to achieve the maximal anesthetic effect of fentanyl.

Patients receiving sufentanil experienced chest wall rigidity more frequently than did patients receiving fentanyl, but the use of vecuronium versus pancuronium had no effect upon rigidity. Sufentanil's faster anesthetic onset may account for this (4,12). Particularly when compared with previous reports using slower narcotic inductions, muscle rigidity was not clinically troublesome with any of the four techniques we used (4,8,49). We believe that pretreatment with a small dose of nondepolarizing muscle relaxant would effectively prevent rigidity with all four techniques (50,51).

We conclude that the fentanyl/pancuronium combination provided the greatest overall hemodynamic and electrocardiographic stability without producing myocardial ischemia, whereas the sufentanil/vecuronium combination most frequently produced hemodynamic depression. Pancuronium was associated with less hypotension or bradycardia than was vecuronium, but was associated with arrhythmia when administered with sufentanil. We disagree with the recommendation that pancuronium be avoided as the

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sole muscle relaxant during the induction of high-dose fentanyl anesthesia (10). Judging from the recent study of Cozanitis et al. (29), perhaps the narcotic/vecuronium combination should be routinely preceded by an anticholinergic agent. However, Paulissian et al. (27) premedicated 22 CABG patients with 6 μ g/kg of scopolamine intramuscularly before inducing anesthesia with fentanyl and vecuronium and still experienced bradycardia (HR < 45) in 4 patients. We prefer to avoid combinations of sufentanil and vecuronium in cardiac surgical patients and believe that this drug combination should be used only with full cognizance of its potential for hypotension and bradycardia.

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Comparison of Bupivacaine and Alkalinized Bupivacaine in Brachial Plexus Anesthesia

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BEDDER MD, KOZODY R, CRAIG DB. Comparison of bupivacaine and alkalinized bupivacaine in brachial plexus anesthesia. Anesth Analg 1988;67:48–52.

To define the effect of alkalinization of bupivacaine 0.5% in subclavian perivascular brachial plexus blockade, the time to onset, time to peak effect, and 6-hour regression of sensory and motor blockade were determined. Sixty physical status ASA I and II patients were randomly allocated to one of two groups and a double-blind design was used: group I (n = 30) received bupivacaine 0.5% (pH, 5.5) 3 mg/kg, waite group II (n = 30) received alkalinized bupivacaine 0.5% (pH, 7.05–7.15) 3 mg/kg. Onset and regression of sensory blockade were determined by pinprick in the C4–T2 skin dermatomes, while motor blockade was assessed using a scheme of proximal to distal muscle group paralysis. Tane to onset of sensory blockade (group I, 4.0 ± 1.2 min; group

II, 3.6 ± 0.9 min) and time to peak sensory effect (group 1, 17.7 ± 1.8 min; group II, 16.3 ± 1.8 min) did not differ significantly between the groups. Similarly, no difference in time to onset of motor blockade (group I, 6.9 ± 1.7 min; group II, 6.3 ± 1.5 min) or time to peak motor effect (group I, 18.1 ± 1.9 min; group II, 15.1 ± 1.9 min) was observed. Regression of postoperative sensory and motor blockade was similar in both groups. It is concluded that alkalinization of bupivacaine 0.5% solutions does not confer any added clinical advantage in subclavian perivascular brachial plexus blockade when compared with commercially available bupivacaine.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus block. ANESTHETICS, LOCAL—bupivacaine.

Ritchie et al. (1-3) confirmed that the cation is the anesthetically active form of a local anesthetic and that the uncharged molecule is essential for penetration to the intracellular receptor site. Using an in vitro model, they demonstrated that alkaline local anesthetic solutions are more effective in sheathed preparations and neutral local anesthetic solutions are more effective in desheathed preparations. Bupivacaine 0.5% (Marcaine) has a pKa of 8.1. In solution it is pH-adjusted to 4-6.5 and exists primarily as the cation at this pH. Increasing the pH of solution before injection increases the amount of bupivacaine existing in the uncharged form and may produce more rapid diffusion across perineuronal tissue barriers. A more rapid onset of clinical blockade should occur. Clinical studies by Galindo (4) concluded that pHadjusted solutions of local anesthetics (pH 7-7.4) produced a more rapid onset of blockade with better

quality and duration than do unmodified commercial preparations. Recently, pH-adjusted bupivacaine was studied using a prospective randomized double-blind design in epidural analgesia for parturients (5). That study used 0.25% bupivacaine with the pH increased from 5.65 to 7.26. Time to onset of sensory blockade was reduced while time to reach peak effect was unaffected with alkalinization. A statistically significant increased duration of analgesia was observed (79.4 vs 96.5 min) with alkalinized bupivacaine 0.25%.

Hilgier (6) in a double-blind study compared 0.5% bupivacaine with epinephrine 1:200,000 (pH 3.9) with an alkalinized solution of bupivacaine with epinephrine 1:200,000 (pH 6.4) when used for brachial plexus block. He reported that alkalinization of the bupivacaine solution increases onset and prolongs duration of sensory blockade. However, Hilgier's results may be open to question because failed or partial blocks were not mentioned.

In the present study, we attempt to define the role of alkalinization of bupivacaine 0.5% on clinical efficacy, onset, and regression in patients undergoing

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Table 1. Study Population*

Group	Anesthetic	Age (yr)	Height (inches)	Weight (kg)	Male/female ratio
I(n = 30)	Bupiyacaine	40 ± 3	68 ± 1	68 ± 1	19/11
II $(n = 30)$	Alkalinized bupivacaine	37 ± 2	67 ± 1	69 ± 2	22/8

*P = NS

Values expressed as mean (± SEM).

upper extremity surgery with subclavian perivascular brachial plexus blockade.

Methods

Following approval by the Human Ethics Committee for Research at the University of Manitoba and the Health Protection Branch, Health and Welfare Canada, informed consent was obtained from patients undergoing upper extremity surgery either on an elective or an emergency basis. Premedication consisted of diazepam 0.10 mg/kg IV 5-10 minutes before performing the block. All patients underwent supraclavicular brachial plexus blockade using Winnie's subclavian perivascular technique (7). Either the standard formulation of bupivacaine 0.5% (Winthrop-Marcaine) or the pH-adjusted preparation was injected in a randomized double-blind manner. The pH-adjusted bupivacaine was prepared immediately before injection by the addition of 0.1 ml of 8.4% (wt/vol) sodium bicarbonate to 20 ml of 0.5% bupivacaine using a tuberculin syringe and a #22 needle. The bicarbonate was added directly into the bupivacaine solution and the bupivacaine/bicarbonate mixture was inverted, without shaking, 30 times over approximately 45-60 seconds. The single batch lot of bupivacaine at pH 5.5 and a final adjusted pH of 7.05-7.15 was determined by Winthrop Laboratories. Neither bupivacaine solution contained epinephrine.

Sixty ASA physical status I or II patients were randomly assigned to one of two groups. Group I received 3 mg/kg of standard 0.5% bupivacaine while patients in group II received 3 mg/kg of pH-adjusted bupivacaine. The amount of bicarbonate added (0.1 ml/20 ml bupivacaine) only marginally changed the concentration of the bupivacaine solution.

Patients between the ages of 16 and 65 years were included in the study. Exclusion criteria included:

- Serious illnesses such as uncontrolled diabetes mellitus, cardiovascular, pulmonary, or renal disorders in which local anesthesia was considered to expose the patient to increased risk.
- History of adverse reactions to local anesthetic drugs.

- 3. Weight <45 kg or >85 kg.
- 4. Patients with circulatory instability.
- 5. Patients requiring local anesthesia on sites other than the study limb.

Both the patient and the investigator making the observations were unaware of the pH of the drug administered.

The blinded observer recorded the onset of sensory block using pinprick in skin dermatomes C4–T2 at 1, 3, 5, 10, 15, 20, and 30 minutes after the completion of injection of the anesthetic solution. Responses were recorded as either aware or not aware of pinprick at each time interval.

Motor block was assessed by the same observer at the same time intervals according to the following scheme: 0, no motor block; 1, inability to abduct the upper extremity or to flex the forearm against resistance; 2, inability to abduct the upper extremity or to flex the forearm against gravity; 3, inability to abduct the upper extremity and to flex the forearm and hand against gravity.

Pulse and blood pressure were also recorded 5, 10, 15, 20, and 30 minutes during onset of anesthesia. In patients with a block satisfactory for the surgical procedure, postoperative measurements were made at 30-minute intervals using sensory and motor testing described above. Measurements were made for 6 hours after the block or until both sensory and motor function had returned.

Patient groups were compared using χ^2 analysis to confirm satisfactory randomization. The results were analyzed using one-way ANOVA. Post-ANOVA multiple comparisons were performed using Duncan's Test. A value of P < 0.05 was considered statistically significant.

Results

The two groups were similar in age, height, weight, and sex distribution (Table 1). Blood pressure and heart rate were similar in the two groups and did not change significantly during the study. Of the 30 patients in group I, 23 (77%) had analgesia adequate for surgery, whereas in group II, 24 (80%) had ade-

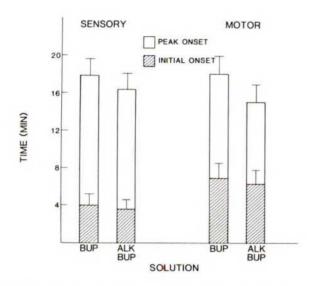


Figure 1. Onset of blockade (n=27 in each group). Values expressed as mean (\pm sem); P=NS. Abbreviations: Bup, commercial bupivacaine 0.5%; Alk. Bup, alkalinized bupivacaine 0.5%.

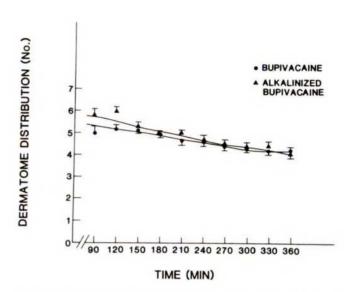
quate analgesia. In group I, in three patients the block failed, whereas four had partial analgesia; in group II, in three patients the block failed and three had partial analgesia. These success rates appear comparable to current studies in the literature (8,9). The three patients in each group with a failed block were eliminated in determining onset time, time to peak effect, and regression of blockade.

Time to onset of sensory blockade (group I, 4.0 ± 1.2 min; group II, 3.6 ± 0.9 min) and time to peak sensory effect (group I, 17.7 ± 1.8 min; group II, 16.3 ± 1.8 min) did not differ significantly in the groups (Fig. 1). Similarly, no difference in time to onset of motor blockade (group I, 6.9 ± 1.7 min; group II, 6.3 ± 1.5 min) or time to peak motor effect (group I, 18.1 ± 1.9 min; group II, 15.1 ± 1.9 min) was observed. Regression of postoperative sensory blockade was similar to both groups, sensory blockade having regressed 1.5 dermatomes 6 hours after the block (Fig. 2). Regression of motor blockade was not observed in either group during the 6-hour postblock assessment (Fig. 3).

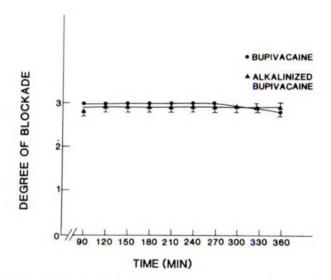
No instance of central nervous system or cardiovascular toxicity was observed in either group during the study. The only complication was a pneumotherax requiring chest tube drainage (incidence 1.6%).

Discussion

Recent studies (5,10) have reviewed the physiochemical basis of altered pH on local anesthetic solutions. The lower the pH, the more charged cations in



<u>Figure 2</u>. Regression of sensory blockade postoperatively starting 90 minutes after performing the block (n = 27 in each group). Values expressed as mean (\pm sem); P = NS.



<u>Figure 3</u>. Regression of motor blockade postoperatively starting 90 minutes after performing the block (n = 27 in each group). Values expressed as mean (\pm sem); P = NS.

solution, whereas an increase in pH results in a greater proportion of the free base form. Ritchie et al. (1–3) postulated that the uncharged base form is more soluble in connective tissue than is the cationic form and more readily diffuses through the nerve sheath. The positively charged cation binds to intracellular receptor sites and blocks nerve conduction once diffusion has occurred (11).

Our results indicate that modifying commercially available 0.5% bupivacaine (Marcaine, Winthrop) without epinephrine using 0.1 ml of sodium bicarbonate per 20 ml does not shorten onset time or decrease time to peak effects with the subclavian

perivascular brachial plexus block. Previous work by Hilgier in which a beneficial effected was demonstrated compared alkalinized bupivacaine with epinephrine (pH 6.4) to 0.5% bupivacaine with epinephrine (pH 3.9) (6). Our study compared alkalinized bupivacaine without epinephrine (pH 7.05-7.15) and stock bupivacaine without epinephrine (pH 5.5). The epinephrine-containing bupivacaine solutions in Hilgier's study had an initial lower pH than did the plain bupivacaine solution employed in our study and, with the addition of 0.2 ml NaHCO₃ solution, underwent a proportionally greater change in pH. This may have accounted for the difference in results. However, in a study comparing pH-adjusted lidocaine solutions for epidural anesthesia (10), there was an inverse relation to the pH of the epidural lidocaine solution injected and the time of onset of analgesia. This was not seen in our study and may be a reflection of comparing the epidural space to the brachial plexus, or of comparing local anesthetics with differing physiochemical properties.

In addition to the inherent problems associated with comparing the effects of alkalinization on different local anesthetic agents used in different sites, onset and duration may be influenced by the concentration of the local anesthetic used (12). In the study by McMorland et al. (5), alkalinization of bupivacaine 0.25% for epidural anesthesia resulted in a more rapid onset and prolonged duration of blockade. In our study, the use of alkalinized bupivacaine 0.5% in supraclavicular brachial plexus blockade did not produce a beneficial effect, although total duration of blockade was not studied. The differences in results in these studies may be in part related to the marginal beneficial clinical effects of alkalinization of regular bupivacaine that become obscured when higher concentrations are employed.

Previous studies (9,13) have demonstrated a more rapid development of motor blockade as opposed to sensory blockade with one study using 50 ml of 0.5% bupivacaine with the subclavian perivascular technique. Winnie et al. (13) attributed this to the arrangement of motor fibers in the mantle and sensory fibers in the core of the trunks and cords. The local anesthetic would therefore diffuse first through the motor fibers and block them before blocking of the sensory fibers. Time to onset of sensory and motor blockade did not differ significantly between the groups in our study. Sensory blockade was determined by Lanz et al. and in our study by using the response to pinprick in the primary innervation zones. Lanz et al. (9) used the following rating scale for motor blockade: 0, normal contraction; 1, reduced contraction (paresis); and 2, no contraction (paralysis). Their results showed that in all instances motor blockade developed more rapidly than sensory blockade. In the evaluation of motor block, paresis and paralysis were combined for simplification by Lanz et al. This may have overestimated the percentage of motor blockade as evaluated at 5 and at 20 minutes. At 20 minutes there was virtually 100% motor blockade in the study by Lanz et al., with our time to peak onset being nearly equivalent to theirs at 17 minutes.

Bupivacaine has been reported to cause cardiotoxicity in both clinical and experimental settings (14–16). We used 3 mg/kg of bupivacaine and observed no signs or symptoms of local anesthetic toxicity. This finding is similar to previous studies and reports using volumes of 40–50 ml of 0.5% bupivacaine (6,9,17,18).

In conclusion, the pH adjustment of commercial bupivacaine 0.5% solutions for subclavian perivascular brachial plexus blockade does not confer any clinical advantage. The use of 3 mg/kg of bupivacaine in this technique has once again been shown to be a safe and effective agent, providing proper technique and precautions are followed.

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Recovery Scores Do Not Correlate with Postoperative Hypoxemia in Children

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SOLIMAN IE, PATEL RI, EHRENPREIS MB, HANNALLAH RS. Recovery scores do not correlate with postoperative hypoxemia in children. Anesth Analg 1988;67:53–6.

The correlation between the degree of postanesthetic recovery (PAR) in children as measured by a modified Aldrete scoring system and oxygen saturation (Sao₂) was studied. Eighty-one ASA PS I unpremedicated infants and children were studied. Oxygen saturation and PAR scores were recorded on arrival in the recovery room, then at 5-minute-intervals. Patients with Sao₂ < 95% were given supplemental oxygen. The proportion of children with Sao₂ <

95% and ≥95% was not significantly different among patients with low PAR scores (≤6) and those with high scores (7–10) in any age group. Similarly, the magnitude of Sao₂ increase after oxygen supplementation did not seem to correlate with increasing wakefulness; i.e., higher PAR scores. It is concluded that children recovering from anesthesia can become hypoxemic in the recovery room. The degree of wakefulness as measured by a PAR score cannot be used to establish an end point for oxygen supplementation. Oxygen supplementation and/or Sao₂ monitoring are recommended in all children recovering from anesthesia.

Key Words: HYPOXIA—postoperative. ANESTHESIA—pediatric.

Motoyama and Glazener (1) recently used the pulse oximeter to show that children recovering from general anesthesia may have arterial oxygen desaturation. Mild desaturation sometimes occurs without any clinical signs of hypoxemia. In healthy children they found that mean O₂ saturation (Sao₂) in room air was 93% (equivalent to a Pao₂ of 66 mm Hg). Oxygen saturation improved with oxygen supplementation and with increasing wakefulness. On the basis of these findings, these authors recommended supplementing O₂ in the postanesthesia recovery room until children were more awake. The degree of desired wakefulness, however, was not clearly defined.

The aim of this study was to correlate postanesthesia O_2 saturation in children with the degree of recovery, as indicated by a postanesthesia recovery (PAR) score that is routinely used in our institution,

and to document the stage of recovery at which O₂ supplementation was no longer needed.

Methods

The protocol was approved by the institutional review board and parents were informed about the study. Eighty-one ASA physical status I unpremedicated children undergoing elective surgical procedures under general anesthesia were studied. Children undergoing intraabdominal, intrathoracic, or intracranial procedures were excluded. The modified Aldrete's scoring system (2) was used to evaluate the degree of postanesthetic recovery. Points are assessed and assigned to levels of motor activity, respiration, blood pressure, consciousness, and color on the patients' admission to the recovery room and at frequent intervals thereafter (Table 1). Children should achieve an overall score of 10 to meet discharge criteria. However, a score of 9 is accepted if the subtracted point is due to elevated blood pressure, a common finding in children crying after surgery.

On arrival in the recovery room the patient's recovery score was computed by an independent

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Table 1. Recovery Room Scoring System

Observed parameter	Points scored
Motor activity*	
Active motion, voluntary or on command	2
Weak motion, voluntary or on command	1
No motion	0
Respiration*	
Coughs on command or cries	2
Maintains good airway	1
Requires airway maintenance	0
Blood pressure	
± 20 mm Hg of preanesthetic level	2
>20-50 mm Hg of preanesthetic level	1
>50 mm Hg of preanesthetic levels	0
Consciousness*	
Fully awake or easily aroused when called	2
Responds to stimuli and exhibits presence of protective reflexes	1
No response or absence of protective reflexes	0
Color	
Pink	2
Pale, dusky, blotchy	1
Cyanotic	0
Total scores	Maximum 10

^{*}The signs of recovery have been rewritten to allow easier interpretation in children.

observer; and the fingertip sensor of a Nellcor pulse oximeter (model N-100) was placed by one of the investigators to record the initial O2 saturations in room air. The cutoff for the definition of hypoxemia was chosen to be 95% (equivalent Pao, 75 mm Hg). This value was considered to be low in a healthy child recovering from anesthesia and insufficient to meet increased metabolic and respiratory requirements in the immediate postoperative period. Children with O_2 saturations <95% were given O_2 via a "blow-by" system at 10 L/min; patients with Sao₂ ≥95% received no supplemental O2. Continuous measurements of Sao₂ were made and recorded every 5 minutes at a time when the digital display on the oximeter showed a constant value. Supplemental oxygen was continued until patients achieved an Sao2 of at least 95% while breathing room air. Patients were discharged when the discharge criteria, as previously defined, were met and O2 therapy could be discontinued.

The association between the PAR score on arrival into the recovery room and Sao_2 was analyzed using Fisher's exact test, investigating the equality of the proportions of patients with $Sao_2 < 95\%$ and $\ge 95\%$ among PAR scores (≤ 6 and 7–10). The magnitude of this association was measured by Spearman's rank correlation coefficient. Because of possible wide physiologic variability of respiratory function in the study population, these associations are reported for three

age groups; \leq 2 years, 2–4 years, and >4 years. P < 0.05 was considered significant in all cases.

Results

The patients' age distribution ranged between 1 month and 12 years (mean 47 months). Surgical procedures in the study patients included ENT (n=36), urology (n=13), orthopedic surgery (n=3), plastic surgery (n=3), general surgery (n=11), ophthalmology (n=14), and oral surgery (n=1). Anesthesia and surgical times ranged between 10 minutes and 4 1/2 hours (mean approximately 1 hour), and 5 minutes and 4 hours (mean 41 minutes), respectively.

The PAR scores and the oxygen saturations in the three groups recorded on admission to the postanesthetic recovery room before the administration of oxygen, are shown in Table 2. No significant association between PAR scores and O2 saturation was found. A specific pattern of increasing Sao2 with concomitant increase in PAR scores was not evident. Spearman's rank correlations (r_s) were 0.266 for the group 1 month-2 years old, -0.135 for the 2-4 year old group, 0.339 for children older than 4 years, and 0.058 for the total sample. None were significantly different from zero (P > 0.05). The proportion of patients with Sao₂ <95% and ≥95% was not significantly different among those who achieved a low (≤ 6) or a high (7-10) PAR score on arrival to the recovery room in any of the groups (Table 3).

Of the 45 patients who required O_2 supplementation because of low measured Sao_2 , 34 had a recovery score of less than 7 and 11 had a score of 7 or more. After O_2 therapy, the mean increase in O_2 saturation was 4 and 5% for patients who had the low and high PAR scores, respectively. Twelve patients still had an $Sao_2 < 95\%$ at the time they met discharge criteria (PAR score, 9 or 10). All those children, however, eventually attained an oxygen saturation of at least 95% in room air before leaving the recovery room.

Discussion

Arterial oxygen desaturation in the postoperative period can be of particular significance because the level of vigilance may be decreased compared to that present during the intraoperative period. There are several possible reasons for the presence of arterial oxygen desaturation during the recovery period. Residual intravenous or inhalation anesthetic agents may cause respiratory depression (3) and alter the

Table 2. Oxygen Saturation* in the Three Age Groups on Admission to the Recovery Room (No O2)

Age (years)	PAR score	п	Sao ₂ (%)	SEM	Minimum Sao ₂ (%)	Maximum Sao ₂ (%)
≤2	≤6	12	95	0.63	92	99
	7-10	17	94	1.38	94	99
2–4	≤6	25	95	0.82	85	100
	7-10	2	94	2.12	92	95
>4	≤6	20	96	0.73	85	100
	7-10	5	96	0.68	95	98

^{*}Values are expressed as mean ± SEM.

<u>Table 3</u>. Proportion of $SaO_2 < 95\%$ and $\geq 9\%$ Among Patients Who Achieved Low or High PAR Scores in the three Age Groups

		Sao		
Age (years)	PAR score	<95	≥95	P Value
≤2	≤6	5	7	>0.9
	7-10	6	11	
2-4	≤6	7	18	>0.5
	7-10	1	1	
>4	≤6	6	14	>0.25
	7-10	0	5	

ventilatory response to hypoxia and hypercapnia (4). Delay in the return of full neuromuscular activity may inhibit the ventilatory effort necessary to overcome mild airway obstruction (3) or to allow coughing to clear accumulated secretions. A reduced functional residual capacity and perhaps airway closure during tidal breathing may predispose the infant or young child, who is breathing spontaneously and unassisted, to arterial oxygen desaturation after anesthesia and surgery (5). Intraoperative hyperventilation and the associated alkalosis may predispose the patient to a lower minute volume with subsequent hypercarbia, increased alveolar-arterial oxygen tension difference, arterial oxygen desaturation, and even hypoxemia during the period of unassisted spontaneous ventilation. Hypothermia and shivering in the postoperative period increases oxygen consumption and decreases Pvo, which can further exaggerate hypoxemia in children. Room air may provide an inadequate oxygen mixture at this juncture in the recovery room.

The pulse oximeter is a noninvasive device that can be used for the detection of early hypoxemia before the development of such clinical signs as cyanosis and bradycardia (6,7). Cyanosis may not be clinically obvious or easily detectable because of factors such as increased skin pigmentation, reduced lighting, anemia, or poor peripheral perfusion (7). Motoyama and Glazener (1) used the pulse oximeter to demonstrate that children recovering from anesthesia can become hypoxemic even in the absence of

any clinical evidence. They also found that children who were more asleep had lower oxygen saturations. Increasing wakefulness seemed to be associated with higher oxygen saturations irrespective of whether or not the child was crying. Recommendations were made, based on these findings, to raise the inspired exygen concentration until children were more awake. Several PAR scores have been devised (2,8) to evaluate the degree of patient wakefulness in the recovery room. A postanesthesia recovery room (PAR) score was postulated to be an appropriate means of determining the end point of oxygen supplementation. In this study, PAR scores did not correlate with oxygen saturations on admission to the recovery room, i.e., while patients were breathing room air. Aldrete (2) had originally suggested that a score of over 7 indicated that patients were ready for safe discharge from the recovery room. We did not observe any difference in the response to oxygen therapy of children with scores of 7 and above and those with scores below 7. The degree of increase of oxygen saturation in response to oxygen administration, therefore, could not be predicted by the PAR score. The most disconcerting finding was that 12 patients with a PAR score of ten, hence fulfilling our discharge criteria in children, still had oxygen saturations <95%. A resolving upper respiratory infection, shivering due to hypothermia, or splinting secondary to pain can be possible explanations for this observation.

In conclusion, our study confirms previous findings that children recovering from anesthesia can become hypoxemic in the postanesthesia recovery room. We, however, could not determine any correlation between the PAR score currently used as a measure of wakefulness (and appropriate conditions for discharge) and oxygen saturation as measured by the pulse oximeter. Therefore, we recommend that unless oxygen saturation is monitored, all children should receive supplemental oxygen in the recovery room. Children who are awake and yet not adequately saturated should be evaluated for other

causes of hypoxemia and monitored with the pulse oximeter for a longer period of time. Future studies might assess whether oxygen saturation monitoring should be included among other discharge criteria of PAR scoring systems.

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In Vitro Effect of Fresh Frozen Plasma on the Activated Coagulation Time in Patients Undergoing Cardiopulmonary Bypass

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BARNETTE RE, SHUPAK RC, PONTIUS J, RAO AK. In vitro effect of fresh frozen plasma on the activated coagulation time in patients undergoing cardiopulmonary bypass. Anesth Analg 1988;67:57–60.

The in vitro effect of fresh frozen plasma (FFP) on the whole blood activated coagulation time (ACT) was examined in 18 patients undergoing cardiopulmonary bypass (CPB) during coronary artery bypass graft surgery. The addition of FFP to whole blood in vitro, after systemic heparinization, significantly prolonged the ACT from 451 \pm 21 seconds (mean \pm sE) to 572 \pm 41 seconds (P < 0.05). There was no

significant correlation between the plasma antithrombin III activity and the prolongation in ACT after systemic heparinization, with or without addition of FFP. The addition of FFP to whole blood in three of the six patients who exhibited heparin resistance (ACT <400 seconds after administration of 350 unit/kg heparin) did not prolong the ACT to >400 seconds. These observations suggest that infusion of FFP will further prolong the ACT after heparin administration in most patients including some with initial heparin resistance.

Key Words: BLOOD, coagulation—activated coagulation time. SURGERY—cardiovascular.

Resistance to the anticoagulant action of heparin during cardiopulmonary bypass (CPB) is a serious concern and a poorly understood phenomenon. Although in most instances the desired prolongation in the activated coagulation time (ACT) is achieved by administration of additional heparin, this has not always been successful (1). Previous exposure to heparin (2,3) or a deficiency in antithrombin-III (AT-III) (1) have been suggested as possible causes. Administration of two units of fresh frozen plasma (FFP) to patients who demonstrated heparin resistance resulted in normalization of their heparin-ACT dose response curve and a decrease in total heparin requirements during CPB (4). These observations may be related to repletion of a deficient plasma factor such as AT-III. The present investigation was designed to determine the in vitro effect of the addition of FFP on the whole blood ACT, and to investigate a possible relation with AT-III activity.

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Methods

This study was approved by our institutional Human Research Review Committee. Eighteen patients (6 women, 12 men) ages 43 to 78 years (mean 58) who underwent coronary artery bypass graft (CABG) surgery gave written informed consent to participate in the study. Patients with preoperative abnormalities in the prothrombin time or the activated partial thrombopastin time, or patients who had received anticoagulants or antiplatelet drugs for up to 1 month before surgery were excluded. Routine monitoring required for the management of these patients included insertion of peripheral arterial and triplelumen flow-directed pulmonary artery catheters. All blood samples were drawn from the arterial line after disgarding the initial 10 ml of blood. Premedication consisted of diazepam 5 to 10 mg PO, scopolamine 0.4 mg IM, and morphine 0.1 mg/kg IM. Anesthesia was induced and maintained with a high-dose narcotic technique involving fentanyl, pancuronium, and oxygen (Fio., 1.0). Mechanical ventilation maintained normocarbia.

Three ACTs were performed immediately before and five minutes after administration of 350 unit/kg porcine heparin (Elkins Sinn Inc.). The first was a whole blood ACT (2.0 ml) without additives; the second and third were measured in whole blood (1.8

ml) with added FFP (0.2 ml) or saline (0.2 ml) as control. In all of the studies reported here the FFP added was from the same unit that had been thawed and stored as multiple 1-ml aliquots at -70°C. The AT-III activity in the additive FFP was within normal limits (80-113%). ACT was determined by rotating whole blood at 37°C in glass tubes in the presence of diatomaceous earth and a small magnet, in a Hemachron (International Technidyne Corporation, Edison, NJ). To insure that the time delay inherent in sequential measurements was not a source of error, whole blood ACTs were performed on additional blood samples obtained 20 minutes after heparin administration and compared with the ACT values of samples obtained 5 minutes after heparin administration. Plasma AT-III activity was measured using a chromogenic substrate S-2238 (Helena Laboratories, Beaumont, TX) (5) in blood samples obtained immediately before the administration of heparin.

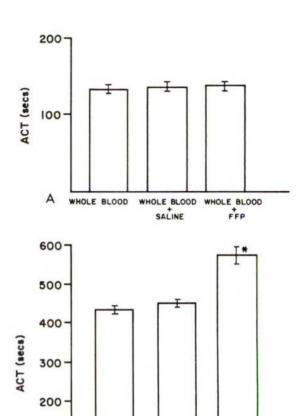
All data are expressed as means \pm sE. The paired Student's *t*-test was used for analysis of ACT data. A *P* value <0.05 was considered significant. Correlations between plasma AT-III activity and the postheparin ACT values were examined by linear regression analysis using the method of least squares. Heparin resistance was defined by prolongation of the whole blood ACT to <400 seconds (6) after administration of 350 unit/kg heparin.

Results

The addition of FFP or saline to preheparin samples did not result in significant prolongation of the ACT (Fig. 1A). Addition of FFP, but not saline, to postheparin samples resulted in an increase in ACT from 451 ± 21 to 572 ± 41 seconds, P < 0.05, (Fig. 1B). In control experiments no significant difference was observed between ACTs from whole blood samples drawn at 5 and 20 minutes after heparinization of the patient.

Six of the 18 patients studied exhibited heparin resistance with a postheparin ACT of 346 ± 45 seconds compared with a postheparin ACT of 470 ± 18 seconds in the remainder. In all six patients there was further prolongation of the ACT on addition of FFP (Fig. 2). However, in three of these patients, the ACT failed to prolong to 400 seconds or greater after addition of FFP (responders, 496 ± 66 seconds; non-responders, 371 ± 48 seconds). These three patients had the shortest postheparin ACT without added FFP.

The relation between the plasma AT-III activity and the prolongation of the ACT after systemic



<u>Figure 1</u>. Effect of the in vitro addition of FFP or saline on the whole blood ACT. (**A**) Before systemic administration of heparin, no prolongation of the ACT was observed. (**B**) Addition of FFP but not saline after systemic administration of heparin resulted in significant prolongation of the ACT (P < 0.05).

WHOLE BLOOD

SALINE

WHOLE BLOOD

heparin administration was examined in heparinresponsive and -resistant patients and no significant correlation was found. Similarly, there was no significant correlation between plasma AT-III activity and the ACT of postheparin samples supplemented with FFP (Fig. 3).

The mean plasma AT-III activity in the patients in this investigation was $79 \pm 4\%$, which is significantly lower (P < 0.05) than that obtained in a group of normal subjects (n = 11) consisting of laboratory personnel between the ages of 20–50 years ($96 \pm 2\%$).

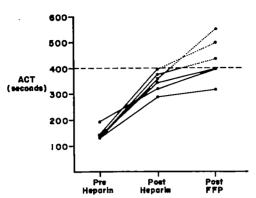
Discussion

100

В

WHOLE BLOOD

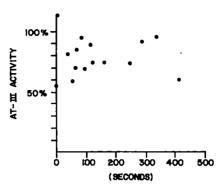
The in vitro addition of FFP to whole blood significantly prolonged the postheparin ACT in this group of patients undergoing CABG surgery. Dilutional



<u>Figure 2</u>. Effect of the in vitro addition of FFP on the ACT after systemic heparin administration in heparin-resistant patients (n = 6).

effects were not responsible for these results because addition of an equal amount of saline in control experiments failed to prolong the ACT. In a previous study (4), infusion of two units of FFP to heparinresistant patients about to undergo CPB consistently prolonged the ACT into the desired range without administration of additional heparin. The dilutional factor in the study by Sabbagh et al. (4) (260-520 ml FFP added to a blood volume of 3600-5000 ml) is comparable to ours (0.2 ml FFP added to 1.8 ml whole blood). Use of the 0.2 ml dilution of the whole blood ACT in vitro with FFP was an attempt to approximate the conditions of the in vivo study by Sabbagh et al. (4) without exposing patients to the risk of transfusion-related infections. Our study shows the salutary effect of FFP on heparin-induced prolongation of the ACT in both heparin-responsive and -resistant patients. However, this effect was variable and, in contrast to the study of Sabbagh et al. (4), not all of the heparin-resistant patients responded to the addition of FFP with a prolongation of the ACT to 400 seconds or greater (Fig. 2). The difference between the two studies may be related to dissimilar patient populations, definitions of heparin resistance, or ranges of acceptable anticoagulation for institution of CPB.

The choice of 350 unit/kg heparin for anticoagulation of patients before institution of CPB was an arbitrary one, but falls within the usual clinical range of 300–400 unit/kg and well within the range of 200–800 unit/kg previously reported (2). The incidence of heparin resistance may to some extent depend on the initial amount of heparin administered. Patients vary in their sensitivity to heparin, and heparin requirements may span a 12-fold range (7). Thus, a larger initial dose of heparin may have decreased the number of patients designated resistant in this study, but at a cost of overdosing others. Administering an additional 20–50% of the initial



<u>Figure 3</u>. Relation between plasma AT-III activity measured in samples obtained before heparin administration and the prolongation in ACT after in vitro addition of FFP to whole blood samples obtained from systematically heparinized patients.

dose of heparin to resistant patients allowed safe institution of CPB in our study population.

Heparin prolongs the coagulation time by accelerating the inhibition of thrombin by AT-III, the major inhibitor in plasma of serine proteases including thrombin. This has led some investigators to postulate that the prolongation of the ACT after administration of FFP was related to AT-III supplementation (1,2). A recent study examined the effect of administration of AT-III concentrates on heparin consumption in patients undergoing CPB for CABG surgery (8). Results indicated the addition of AT-III led to a significant increase in the sensitivity of their patients to heparin and a significant decrease in heparin consumption. Interestingly, in that study the AT-III activity in plasma samples obtained before heparinization was found to be in the lower range of normal in all patients. This is consistent with our findings and those of another study (9) showing that plasma AT-III activity in patients with coronary artery disease is decreased compared to normal subjects.

In this study, no relation was found between preoperative AT-III levels and the response to the in vitro addition of FFP. This does not mean that the addition of AT-III in FFP was not responsible for the effect, but only that measurement of preoperative AT-III activity does not allow one to predict which patients will respond to FFP. Moreover, plasma factor(s) other than AT-III, e.g., heparin cofactor II (10), may be responsible for the synergistic effect of FFP on ACT prolongation in heparinized patients undergoing CABG surgery. This area needs further exploration.

In summary, the in vitro addition of FFP to whole blood samples obtained after heparin administration from patients about to undergo CABG surgery produced significant augmentation of the ACT. However, in some heparin-resistant patients this effect may not be sufficient to prolong the ACT to levels acceptable for institution of CPB.

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Long-Term Bupivacaine Infusion Does Not Alter the Acute Seizure Threshold to Bupivacaine in Rats

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SKEIE B, MEIDELL NK, STEEN PA. Long-term bupivacaine infusion does not alter the acute seizure threshold to bupivacaine in rats. Anesth Analg 1988; 67:61–3.

Rats were given a continuous subcutaneous infusion of either bupivacaine (n = 18) or placebo (n = 17) for 4 days. On the 5th day the acute seizure threshold to intravenous bupivacaine was determined in both groups. Blood and brain concentrations of bupivacaine at the onset of seizures

showed no difference between the two groups, whereas the seizure dose was decreased in the bupivacaine group. The tachyphylaxis observed when bupivacaine is used for a regional nerve blockade does not seem to evolve for the central nervous system effects.

Key Words: ANESTHETICS, LOCAL—bupivacaine. PHARMACOLOGY—tachyphylaxis. TOXICITY—bupivacine.

The continuous infusion or intermittent injection of local anesthetic agents into the epidural or subdural space has been employed for prolonged surgical procedures or to provide an extended period of postoperative pain relief. However, tachyphylaxis, or acute tolerance, has been observed to occur after the continuous or repeated administration of local anesthetic agents into the subarachnoid or epidural space (1–3). Tachyphylaxis of this type may be defined as a decrease in analgesic response to the repeated injection of a constant dose of local anesthetic. Repeated injections or prolonged infusions of local anesthetic agents may thus be associated with decrease in segmental spread, duration of action, and quality of the nerve blockade (2).

The etiology of local anesthetic tachyphylaxis has not been completely defined. The portion of the local anesthetic dose reaching the receptors may decline with successive injections, or an increase in receptor sensitivity may develop. Local anesthetic agents readily cross the blood-brain barrier to cause central nervous system (CNS) effects. Impulse conduction within the CNS is believed to be blocked through a

membrane-stabilizing action in the same way as in the peripheral nerves (4).

The aim of our study was to determine if tachyphylaxis develops for the CNS effects of bupivacaine by testing whether the seizure threshold of bupivacaine increases in rats pretreated with a subconvulsant dose of bupivacaine over a period of time. A previous study by our group (5) indicated that the CNS toxicity to bupivacaine was not altered after pretreatment with a nontoxic infusion of bupivacaine. However, in that study the blood concentration of bupivacaine during the pretreatment period was low (2-3% of seizure levels) and may not have been sufficient to develop CNS tolerance. Because of the low bupivacaine levels, we found no difference in the acute seizure dose between the placebo- and bupivacaine-pretreated groups. In view of this, we found the present study necessary, to make sure that the results from our first study also were valid when higher bupivacaine doses were given over a period of time before the determination of the acute seizure threshold.

Materials and Methods

Thirty-five young adult (approximately 60 days old) male rats (Mol:WIST) were included in a blind, randomized, and parallel group study. On the first day two osmotic pumps (Alzet model 2ML 1) were implanted subcutaneously under general anesthesia

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(Hypnorm Vet Mekos 0.05-0.1 ml/100 g intraperitoneally) in each rat. The osmotic pumps were filled with either 4 ml bupivacaine (2 ml each) or saline 0.9%. For 4 days the rats lived normally while the osmotic pumps delivered the solution into the tissue (20 μl/hr). On day 5 the rats were weighed and a continuous infusion with bupivacaine (1.25 mg/ml at 20 ml/hr) was started. No other medication was given. When seizures developed clinically, an intracardiac blood sample was drawn, the cranium was opened, and the whole brain was excised. The blood sample and the brain tissue were immediately frozen and stored. There were no problems in collecting 1–2 ml of blood intracardially through a needle into the chestwall when seizures started. The blood samples and the brain tissue were analyzed for bupivacaine per milliliter blood and per gram brain tissue, respectively (ASTRA, Research and Development Laboratories, Sødertelje, Sweden). The brain concentrations of bupivacaine were measured after the whole brain was homogenized at 0°C. Statistical analysis was made using the Wilcoxon two-sample rank sum test. P < 0.05 was considered statistically significant.

Results

A pilot study was first performed in a separate group of rats to establish that the bupivacaine solution entered the bloodstream and the brain tissue from the subcutaneously implanted pumps. Blood concentrations of bupivacaine after 4 days were $0.38 \pm 0.1 \mu g/ml$ (median \pm sp. n = 5) and brain concentrations were $0.3 \pm 0.1 \mu g/g$ (n = 3).

We found no difference in weight on day 5 between the rats pretreated with placebo and these pretreated with bupivacaine (placebo group: $246.8 \pm 42.5 \, \text{g}$, n = 17; bupivacaine group: $247.8 \pm 44.3 \, \text{g}$, n = 18). The seizure dose and the blood and brain concentration of bupivacaine at the onset of seizures in the rats pretreated with bupivacaine and in the placebo group are given in Table 1. There is a statistically significant decrease in the seizure dose (P < 0.02) in the bupivacaine group. There are no differences in blood and brain concentrations of bupivacaine at the onset of seizures between the two groups.

Discussion

Our study indicates that the CNS toxicity evaluated by the seizure threshold of bupivacaine does not change after pretreatment for 4 days with a non-toxic

<u>Table 1</u>. Values at Onset of Seizures for Placebo- and Bupivacaine-Pretreated Groups

	Pretreatment		
	Bupivacaine $(n = 18)$	Placebo (n = 17)	
Bupivacaine dose (mg/kg)	5.2 ± 1.9*	6.6 ± 2.0	
Bupivacaine blood concentration (μg/ml)	$4.0 \pm 1.4^{\dagger}$	4.1 ± 1.3	
Bupivacaine brain concentration (μg/g)	$10.1 \pm 3.3^{\dagger}$	10.2 ± 3.2	

Values are expressed as mean ± sp.

*p < 0.02

tP = NS.

infusion of bupivacaine. The reduced seizure dose in the group pretreated with bupivacaine is explained by the bupivacaine levels in blood before the seizure induction. The rats received the bupivacaine infusion over 4 days, which should be a sufficient period to establish tachyphylaxis. The development of tolerance observed when local anesthetics are used for a regional nerve blockade does not seem to evolve for the CNS effects of bupivacaine. This supports the findings we previously reported (5). In that study, however, the dose of bupivacaine infused before the seizure induction was much lower (blood concentration, $0.08 \pm 0.04~\mu g/ml$), and might have been too low to induce tolerance.

The two groups seemed to behave identically during the study period. We also found no difference in the mean weight between the bupivacaine- and placebo-pretreated groups after 4 days, which indicates that the behavior with regard to eating, drinking, and drowsiness was identical, and that no major electrolyte or metabolic changes took place in the bupivacaine group that might have resulted in an alteration in the seizure threshold of its own. However, we weighed the rats only on day 5 and thus cannot be sure that the groups were comparable with regard to weight at the initiation of the study, even if the rats were in the same age group and had the same sex.

Most of the local anesthetics demonstrate anticonvulsant activity in low doses. The anticonvulsant activity occurs at doses and blood levels considerably lower than the levels associated with seizure activity (4). With higher dosages, however, local anesthetics may produce convulsions. The excitatory effect of local anesthetic agents in the brain involves a selective blockade of inhibitory pathways in the cerebral cortex (6). After this period of CNS excitation, a further increase in the amount of local anesthetic drug administered results in generalized CNS depression.

Local anesthetic drugs act on excitable membranes; in the CNS the inhibition of conduction of nerve

impulses acts to stabilize membranes in the same way as in peripheral nerve membranes (4). We administered the bupivacaine as a peripheral continuous infusion; consequently, no anatomic injuries caused by successive injections or the solution itself occurred in the tissue surrounding the CNS nerves. Assuming that the mechanism of action of bupivacaine in the CNS and in the peripheral nerve system is the same, the lack of tolerance development may indicate that the tachyphylaxis observed for regional blockades is caused by a decrease in the portion of local anesthetic reaching the receptors and not by a reduction at the receptor levels. Several factors may be at work in reducing the dose reaching the nerve membrane (7); important among these are anatomoc causes (edema, local hemorrhage, clot formation, or transudate) that tend to isolate the nerve from contact with the anesthetic solution. Hypernatremia and low pH of the injected solution may also reduce the quantity of anesthetic available for diffusion (2,3). A lowering of the pH tends to decrease the amount of local anesthetic in the base form which is responsible for diffusion through the nerve membrane (3).

We found that long-term bupivacaine infusion does not alter the seizure threshold of bupivacaine. The development of tachyphylaxis during a peripheral nerve blockade depends on the timing of successive doses (2) and the numbers of re-injections required (2,8). If the intervals between injections are long enough to allow analgesia to wear off completely, the next dose will have to be increased by 25–30% above that of its immediate predecessor to maintain a stable level of analgesia (2). Because we have found that the seizure threshold for bupivacaine

does not alter, the resultant need for an increased dose will decrease the therapeutic index (the analgetic/toxic dose). The clinical applications of these findings are that successive doses should be given before the effect of the previous dose has worn off, and that long-acting agents are required to reduce the need for frequent re-injections (8).

We thank ASTRA Lakemedel, Sødertelje, Sweden, for supplying the bupivacaine solution and for performing the analysis of bupivacaine in the blood and brain.

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Neonatal Neurobehavior after Epidural Anesthesia for Cesarean Section:

A Comparison of Bupivacaine and Chloroprocaine

Betty R. Kuhnert, PhD, Mary J. Kennard, BSN, and Patricia L. Linn, PhD

KUHNERT BR, KENNARD MJ, LINN PL. Neonatal neurobehavior after epidural anesthesia for cesarean section: a comparison of bupivacaine and chloroprocaine. Anesth Analg 1988;67:64–8.

Reports of whether or not bupivacaine affects neonatal neurobehavior have been contradictory. The purpose of this study was to test the hypothesis that scores on the Brazelion Neonatal Behavioral Assessment Scale (BNBAS) after epidural anesthesia with bupivacaine for cesarean section would not be different than those after chloroprocaine. Furthermore, if there were any effects, it was hypothesized that they would be related to cord blood levels of the drug. Fifty-five healthy mother/infant pairs were studied. Clinical characteristics, pharmacologic data, and BNBAS scores were obtained and analyzed using statistical techniques that

included t-tests, repeated measures analysis of variance, and stepwise multiple regression. The results indicate that I ifants in the bupivacaine group do significantly better than those in the chloroprocaine group in the orientation cluster of the BNBAS (F[1,49]=22, P<0.001); this cluster reflects higher cortical functioning. Furthermore, there was improvement in the bupivacaine group in the regulation of state cluster with age, whereas there was no improvement in the chloroprocaine group (F[1,53]=4.34, P<0.01). This study suggests that performance on the BNBAS after exposure to bupivacaine is better than that after exposure to chloroprocaine.

Key Words: ANESTHESIA—obstetric. ANESTHETICS, LOCAL—bupivacaine, chloroprocaine.

Bupivacaine is used almost exclusively for obstetric epidural anesthesia in many institutions. Several of the reasons that it is favored are 1) its metabolites are probably inactive, 2) little active drug is thought to reach the infant because of the extensive binding of the drug to maternal plasma proteins, and 3) it has a long duration of action and good dissociation between sensory analgesia and motor blockade. However, considerable placental transport has been demonstrated (1,2). Because bupivacaine does cross the placenta, it is important to know if it has any adverse neurobehavioral effects on the infant.

Despite its widespread use, particularly for cesarean section, there is lack of agreement as to whether bupivacaine has adverse neonatal neurobehavioral effects (3). None of the studies using the Scanlon Early Neonatal Neurobehavioral Scale (ENNS) (4) or the Neurologic and Adaptive Capacity Scoring System (NACS) (5) has demonstrated any adverse effects due to bupivacaine (6–8), except for a depression of the sucking response at 24 hours (9), or any differences between bupivacaine and chloroprocaine (7). On the other hand, significant and consistent longterm neonatal effects of bupivacaine have been reported using the Brazelton Neonatal Neurobehavioral Assessment Scale (10) (BNBAS) (11,12).

All of these previous studies have been criticized because of inappropriate control groups, inappropriate data analysis, or lack of attention to confounding clinical variables (3). To resolve this controversy, our purpose was to determine whether bupivacaine has any adverse effects on the BNBAS when compared with chloroprocaine and whether these effects are related to cord blood bupivacaine levels.

Materials and Methods

Fifty-five infants delivered by elective cesarean section under epidural anaesthesia were studied. Twen-

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ty-nine of the mothers received bupivacaine (23 received 0.5%, 7 received 0.75%), and 26 received chloroprocaine (3%). The local anesthetics did not contain epinephrine and the mothers were not premedicated. The chloroprocaine subjects (except for one patient) were historical controls (13) because chloroprocaine is currently used infrequently at our institution. All parturients were at term with uncomplicated pregnancies and delivered normal infants. The study was approved by the Human Investigation Committee of Cleveland Metropolitan General Hospital, and informed consent was obtained from each mother before surgery.

Because a nonmedicated control group cannot exist for cesarean sections, chloroprocaine was chosen for the "control" group. This seemed reasonable because a previous study in vaginally delivered infants exposed to chloroprocaine suggested that their performance on the BNBAS was very similar to those delivered without medication (14).

Clinical characteristics and pharmacologic data were recorded for each patient. These included maternal age, race, gravidity, parity, neonatal gestational age, Apgar scores at 1 and 5 minutes, birth weight, cord vein pH, sex of the infant, drug used for epidural anesthesia, together with concentration, number of injections, total milligrams administered, drug-to-delivery time interval for the first and last dose (DDI), and cord vein drug levels. Local anesthetic levels in cord blood were measured as reported previously (1,15).

Examinations using the BNBAS were also performed as reported previously (13,16). All infants were tested twice, once at <12 hours of age and once at 3 days of age. The same examiner or an examiner with established reliability with the primary examiner took part in both studies. Performance was scored using the seven a priori behavioral clusters suggested by Lester et al. (17). These include clusters of the habituation, orientation, motor, range of state, regulation of state, autonomic regulation, and number of abnormal reflexes.

The data were analyzed in the following manner. First, clinical and pharmacologic variables of the two patient groups were compared by *t*-tests and significantly different confounding clinical variables that might affect cluster scores were noted between the groups. Next, whether infants exposed to bupivacaine differed from the chloroprocaine group was addressed using a repeated measures analysis of variance controlling for significant confounders noted in the *t*-tests. This analysis was designed to determine whether the Brazelton scores were affected by drug choice, time when the BNBAS scores were

<u>Table 1</u>. Maternal Characteristics ($X \pm sD$)

Characteristics	Chloroprocaine $(n = 26)$	Bupivacaine $(n = 29)$	P = Value
Age	25 ± 5	28 ± 6	0.04
Gravidity	3.5 ± 1.4	2.9 ± 1.3	NS (0.07)
Parity	1.8 ± 0.8	1.7 ± 1.2	NS
Hypotension N (%)	6 (23)	7 (24)	NS

Table 2. Neonatal Characteristics ($X \pm sD$)

Characteristics	Chloroprocaine $(n = 26)$	Bupivacaine $(n = 29)$	P Value
Gestational age (weeks)	39 ± 0.9	39 ± 1.3	NS
Bi_thweight (g)	3381 ± 471	3355 ± 502	NS
Apgar <7 at 1 minute	0	1 .	
Apgar <7 at 5 minutes	0	0	
Cord vein pH	7.30 ± 0.05	7.32 ± 0.05	NS
Sex		•	
Male	16	12	
· Female	10	17	
Age at first examination (hours)	3.1 ± 1.3	3.4 ± 2.5	NS

obtained, or an interaction between the two. For those clusters where differences were noted, stepwise multiple regression was used to determine whether cord vein drug levels affected scores on the individual clusters when confounding clinical variables were controlled. A difference in cluster scores of at least one scale point (18) and a P < 0.05 were required for establishing statistical significance.

Results

The clinical characteristics of the mothers and neonates are shown in Tables 1 and 2. Mothers who received chloroprocaine were somewhat older and of higher gravidity but not parity. For these reasons, gravidity and age were used as covariates in the repeated measures analysis of variance and in the stepwise multiple regression for each cluster where differences between the groups were found.

The pharmacologic characteristics of the two groups are shown in Table 3. It was expected that these variables would be different based on the characteristics of the two drugs. The difference in the time between delivery and the last dose of the drugs was examined as a potential confounding variable.

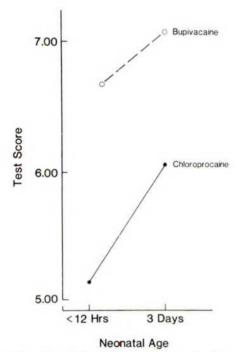
Choice of drug was statistically significant and resulted in a difference of at least one scale point for the orientation cluster (F[1,49] = 22, P < 0.001) (Fig. 1). Neonates in the bupivacaine group performed better than those in the chloroprocaine group. This

1

<u>Table 3</u>. Pharmacologic Characteristics of Study Population ($X \pm sb$)

	Chloroprocaine	Bupivacaine	P Value
Number of doses	2.3 ± 1.1	1.3 ± 0.5	0.0002
Dosage (mg) DDI*	847 ± 231	138 ± 34	0.00001
First	43 + 23	41 ± 11	N5
Last	22 ± 12	31 ± 16	0.01
Cord vein drug levels (ng/ml)	5 ± 1	288 ± 13	0.00001

*Drug to delivery intervals (min) between first and last injections of epidural local anesthetics.



<u>Figure 1</u>. The effect of drug choice on orientation cluster performance.

was true even when parity, age, and final drug to delivery interval were entered as covariates. Standard deviations for the first and second examinations were 1.5 and 1.1 for infants in the chloroprocaine group and 1.4 and 0.9 for infants in the bupivacaine group, respectively. No significant correlation could be found between cord vein bupivacaine levels and performance on the orientation, cluster. The interval between the last epidural injection and delivery did account for a significant percentage of the variance in performance on the <12 hour examination when stepwise multiple regression was used (F[7,16] = 7.5,P < 0.001). Twenty percent of the variance was accounted for; the longer the interval between the last injection of local anesthetic and delivery, the poorer the test score.

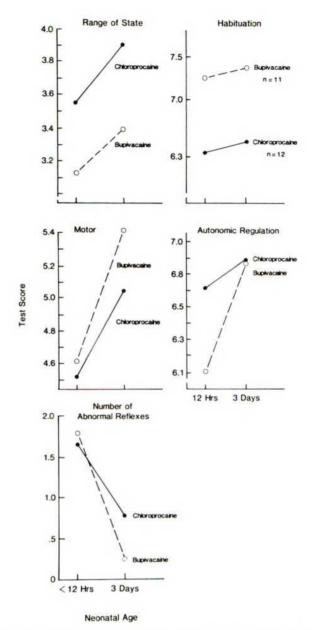


Figure 2. Effect of age on performance on the Brazelton clusters.

Figures 1, 2, and 3 summarize the results of the repeated measures analysis of variance. Both groups of neonates had statistically significant improvements in test scores with age for the motor, (F[1,53] = 46) reflex, (F[1,53] = 41) autonomic (F[1,53] = 11), and orientation (F[1,50] = 11) clusters. There was marginally significant improvement (F[1,53] = 3.7, P = 0.059) in the range of state cluster. For the regulation of state cluster, there was a significant interactive effect between drug and test day (F[1,53] = 4.34); only the neonates in the bupivacaine group improved (Fig. 3). Standard deviations for the first and second examinations were 1.2 and 1.0 for the

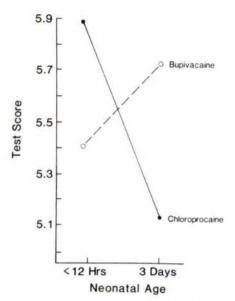


Figure 3. Lack of improvement in regulation of state in the chloroprocaine group.

infants in the chloroprocaine group and 1.1 and 0.9 for the infants in the bupivacaine group, respectively.

In general, there was a trend for the bupivacaine group to perform more favorably than the chloroprocaine group on most of the clusters. This was particularly true for the second exams (Fig. 1, 2, and 3).

Discussion

The purpose of this study was to test the hypothesis that operatively delivered infants whose mothers received epidural anesthesia with bupivacaine would perform as well as those whose mothers received chloroprocaine when confounding clinical and pharmacologic variables were controlled. The results suggest that infants born of mothers delivered under bupivacaine epidural anesthesia do better than do infants delivered under chloroprocaine epidural anesthesia on several clusters of the BNBAS.

Cesarean section deliveries were chosen for study for several reasons. First, all the possible obstetric confounders related to duration of labor, use of forceps, oxytocin, and so on were eliminated. Second, higher doses of epidural local anesthetics are used for cesarean deliveries than for vaginal deliveries. Thus, if effects were to be seen that were due to drug choice alone, they should be more obvious in neonates delivered by cesarean section. However, the disadvantage of the design of the present study is that true, nonmedicated controls are not possible.

The use of an historic control group, although not desirable, was unavoidable in this study; chloropro-

caine is rarely used any more for obstetrical anesthesia in our institution. The present comparisons and conclusions deserve, therefore, to be interpreted cautiously for this reason. However, it should be pointed out that the local anesthetic blood levels were measured in the same laboratory, the same examiner did most of the examinations, and the philosophy of clinical care did not change over the time of data collection. Our institution is a teaching hospital and most of the care in both groups was provided by residents.

Chloroprocaine was a logical choice for a "control" group because of its pharmacology. Whereas bupivacaine is an amide local anesthetic with a long half-life, chloroprocaine is an ester-linked local anesthetic metabolized by plasma cholinesterase. The in vitro halflife of chloroprocaine is measured in seconds and its in-vivo half-life after epidural anesthesia is measured in minutes (19). Thus, only trace levels of active drug reach the infant (20). In a study designed to compare vaginally delivered infants exposed to chloroprocaine with neonates delivered without medication, only one difference was found on either test day for the seven clusters of the BNBAS (vide infra) (14). Thus, chloroprocaine was expected for the present purposes to approximate a "nonmedicated" control group of cesarean-delivered infants. The results of this study suggest that neonates exposed to bupivacaine actually do better than those exposed to chloroprocaine.

The bupivacaine neonates in the present study did clinically and statistically better on the orientation cluster of the BNBAS. The cluster includes orientation to visual and auditory stimulation and alertness. Thus, items that reflect cortical functioning, as opposed to brain stem function (i.e., reflexes), seem to be affected by chloroprocaine. Furthermore, infants exposed to bupivacaine, but not to chloroprocaine, had improved performance with age on the regulation of state cluster. This cluster contains items reflecting cuddliness, consolability, self-quieting, and hand-to-mouth activity that are related to the infant's ability to interact with its caretaker (21). Infants delivered vaginally without medication show improvement on this cluster (14), whereas those delivered vaginally with meperidine (16), chloroprocaine (14), or other drugs (17), or delivered operatively with lidocaine (13) or chloroprocaine (13), do not. Thus, in this cluster, the bupivacaine group is closer to a nonmedicated control group than to any of the other drug groups.

The results of this study are in partial agreement with some of the earlier reports because no adverse effects due to bupivacaine were found on clusters that reflect muscle tone. These findings agree with reports from studies that used either the ENNS or NACS (4,6–8); both of these assessments emphasize muscle tone (4,5). However, in contrast to an earlier study of vaginally delivered infants (12), we could not find any relations between cord vein drug levels of bupivacaine and neurobehavioral performance. This difference may be due to the method of delivery. Clinical factors such as method of delivery (13), length of labor, and so on are well known to influence BNBAS performance (21,22).

It is unclear at this time why exposure to bupivacaine would improve performance on the BNBAS when compared with a drug that barely reaches the fetus in an active form. One could speculate that the metabolites of chloroprocaine (2-chloroaminobenzoic acid or diethylaminoethanol) may be pharmacologically active at the levels occurring after epidural anesthesia. However, at the present time there is no pharmacologic evidence for this speculation. Nevertheless the results of this study support our previous suggestion that chloroprocaine may not be completely innocuous to the infant (14).

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Cimetidine Does Not Affect Plasma Cholinesterase Activity

J. Reddy Kambam, MD, and John J. Franks, MD

KAMBAM JR, FRANKS JJ. Cimetidine does not affect plasma cholinesterase activity. Anesth Analg 1988;67:69–70.

Blood samples were drawn from 10 ASA physical status 1 and 2 patients before (baseline) and after the administration of cimetidine to determine the in vivo effect of cimetidine on plasma cholinesterase (PCHE) activity. The in vitro effects of cimetidine at different plasma concentrations were also studied using the same blood samples. PCHE activity in the baseline samples was 432 ± 4.6 (mean \pm SEM) U/ml, the dibucaine number 82. Administration of oral cimetidine

(300 mg) the night before and 2 hours before surgery, failed to have any effect on PCHE activity (no in vivo effect). Plasma cholinesterase activity in the presence of cimetidine in vitro at plasma concentrations of 1.5, 15, 150, and 1500 μ E/ml was 428, 420, 397, and 177 U/ml, respectively. Thus, in vitro data showed that cimetidine at plasma concentrations (1.5 to 15 μ E/ml) achieved with clinical doses also has no effect on PCHE activity.

Key Words: NEUROMUSCULAR RELAXANTS—succinylcholine. ENZYMES—pseudocholinesterase. HISTAMINE—cimetidine.

We have recently shown that cimetidine potentiates the duration of action of succinylcholine in humans (1). The mechanism by which cimetidine prolongs succinylcholine action is not known. Data from the recent literature also suggest that cimetidine potentiates the central nervous system toxicity caused by 2-chloroprocaine in mice (2). The mechanism for these adverse effects associated with the administration of cimetidine on succinylcholine and 2-chloroprocaine could be that cimetidine inhibits plasma cholinesterase (PCHE) activity. Therefore, we studied the effects of cimetidine both in vitro and in vivo on PCHE activity.

Methods

7

We studied 10 ASA physical status 1 and 2 patients (ages 20–55 years, both sexes) who were to receive oral cimetidine 300 mg at bed time the night before and also 2 hours before the scheduled surgery the following morning. These patients were receiving no other medications known to suppress plasma choli-

nesterase (PCHE) activity. Five milliliters of heparinized blood was collected before the first dose of cimetidine (baseline sample) and also just before the commencement of surgery. Plasma was separated from the blood samples and used for PCHE assay and dibucaine numbers (DN). Plasma cholinesterase activity was also studied in vitro at plasma cimetidine concentrations of 1.5, 15, 150, and 1500 μ g/ml. The baseline plasma samples were used for in vitro studies.

Informed consent was obtained from all the patients with prior approval of our Institutional Review Board for the Protection of Human Subjects. A kinetic method described by Zapf and Coghlan (3) was used in the determination of PCHE activity and DN.

Analysis with one-way analysis of variance (ANOVA) and testing by the Newman-Keuls multiple range test were used to compare the in vitro effects of cimetidine with the baseline. Student's t-test was used to determine the significance of difference between the baseline and postcimetidine (in vivo effect) PCHE activities. A difference was considered significant if P < 0.05. Data are reported as mean \pm SEM.

Results

Table 1 contains the summary of the results. All patients had normal dibucaine numbers (DN values of 80–88). No significant difference in the PCHE

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Table 1. Effect of Cimetidine on PCHE Activity

Group*	PCHE activity (mean ± sem) (U/ml)	P
Baseline	432 ± 4.6	_
In vivo: after cimetidine	438 ± 6.2	N5
In vitro: after cimetidine†		
1.5 μg/ml	428 ± 4.7	NS
15.0 μg/ml	420 ± 5.4	N5
150.0 μg/ml	397 ± 4.2	< 0.05
1500.0 μg/ml	177 ± 6.8	< 0.05

^{*}n = 10 each group.

activity was seen between the plasma samples collected before and after the administration of cimetidine to the patients (in vivo effects), nor was an in vitro effect seen when plasma samples were tested for PCHE activity with cimetidine concentrations (1.5–15 μ g/ml) that are usually achieved when clinically effective doses of cimetidine are administered.

Discussion

Cimetidine, a histamine receptor 2 antagonist, is associated with a relatively low incidence of side effects, but side effects may include bradycardia, hepatotoxicity, interstitial nephritis, and mental confusion (4,5). Although not highly toxic by itself, the effects of cimetidine on the hepatic microsomal enzyme systems and liver blood flow appear to predispose cimetidine to a variety of interactions with several drugs that are inactivated by the liver. Interactions between cimetidine and succinylcholine and local anesthetic drugs are of particular interest to anesthesiologists. Recent data suggest that cimetidine prolongs the duration of action of succinylcholine, an ester type of depolarizing muscle relaxant

that is metabolized primarily by plasma cholinesterase (1). In mice, cimetidine also significantly potentiates the central nervous system toxicity associated with the ester type local anesthetic, 2-chloroprocaine, which is also hydrolyzed by the same plasma cholinesterase that inactivates succinylcholine (2). Because both succinylcholine and 2-chloroprocaine are primarily hydrolyzed by plasma cholinesterase, one might hypothesize that cimetidine inhibits plasma cholinesterase to produce these adverse effects. However, both our in vitro and in vivo data clearly demonstrate that cimetidine has no inhibitory effect on PCHE activity at plasma concentrations achieved with usual clinical doses of cimetidine. These results are not surprising because cimetidine has no known inhibitory effect on nonmicrosomal enzyme systems. Plasma cholinesterase is mainly produced in the liver and is considered a nonmicrosomal enzyme (6). The mechanism by which cimetidine prolongs the duration of action of succinylcholine remains undefined.

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[†]Cimetidine plasma concentrations.

Clinical Reports

Massive Macroglossia and Airway Obstruction After Cleft Palate Repair

Charlotte Bell, мр, Tae Hee Oh, мр, and John R. Loeffler, мр

Key Words: AIRWAY—obstruction. ANESTHESIA—pediatric.

Although significant upper airway problems are encountered after the repair of a cleft palate in patients with certain craniofacial abnormalities (e.g., Treacher Collins syndrome, Turner's syndrome, Pierre-Robin syndrome, Down's syndrome, etc.) (1–3), the anesthetic management of cleft palate repair with an otherwise normal pediatric airway is rarely complicated. However, we recently managed two infants who underwent cleft palate repair and subsequently developed massive macroglossia with upper airway obstruction shortly after extubation. The lifethreatening extent of this airway obstruction and the prolonged postoperative course complicated by aspiration pneumonia provide the basis for the following report.

Case 1

A 17-month-old, 7.4-kg boy was scheduled for elective repair of cleft palate. He was delivered at full term by cesarean section for breech position, and presented other congenital anomalies including a malformed pelvis with absence of both hips and legs. Left inguinal herniorrhaphy at age 3 months and bilateral myringotomies with tubes at age 16 months were performed under uneventful general anesthesia.

Physical examination revealed an alert infant with cleft of the secondary (soft) palate and slight macrognathia, but an otherwise normal airway. Anesthesia was induced with inhalation of nitrous oxide, oxygen and halothane via facemask. The child's trachea was easily intubated. No difficulty was encountered in maintaining the airway either by mask or by endotracheal tube. An intravenous catheter was inserted in the right arm.

Lidocaine 1% (5 ml) with epinephrine 1:100,000 dilution was injected locally into the palate by the surgeon, and a V-Y pushback palatoplasty and intravelar veloplasty was performed using a Dingman retractor for surgical exposure. The intraoperative course was uneventful except for an increase in rectal temperature to 39.7°C when the intravenous fluid catheter became dislodged. A bolus of fluid (200 ml) was infused immediately after replacement of the catheter. Total blood loss was estimated at 20 ml, and 350 ml crystalloid were infused during the 4.5-hour operation.

At the conclusion of the procedure, a bolster was sutured to the upper palate, residual neuromuscular blockade was reversed with atropine 0.15 mg and neostigmine 0.3 mg, and spontaneous ventilation resumed. However, inability to maintain a patent airway required placement of an oral airway after extubation. Subsequent removal of the oral airway resulted in immediate upper airway obstruction and respiratory distress, neither of which was relieved by removal of the bolster.

In the recovery room, progressive engorgement of the tongue and suprahyoid edema increased the threat of airway obstruction. Over the next 2.5 hours, the engorged tongue eventually filled the entire open oral cavity and protruded through the open mouth. The undersurface of the tongue had a weepy, cystic appearance. There was no evidence of allergic reaction such as rash, or generalized edema or erythema.

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Figure 1. Massive lingual and sublingual edema approximately 2 hours after cleft palate repair. (Courtesy of Richard Stahl, M.D.)

The patient was initially tachypneic and agitated with nasal flaring and intercostal retractions. He became progressively stuporous and immediate tracheal reintubation became imperative, successfully accomplished after multiple laryngoscopies. Lung fields were clear immediately after intubation and endotracheal suctioning.

The patient was admitted to the pediatric intensive care unit and mechanically ventilated. After a course of intravenous dexamethasone therapy, he was extubated on the 3rd postoperative day when the lingual and suprahyoid edema had completely subsided. Persistent spiking fever and positive sputum cultures compatible with aspiration pneumonia necessitated antibiotic therapy and further prolonged his hospitalization. He was discharged from the hospital on the 6th postoperative day.

Case 2

A 14-month-old, 10.4-kg girl was scheduled for elective cleft palate repair. Her birth and development were unremarkable except for impediment of phomation and recurrent otitis.

Physical examination was noteworthy for a complete cleft of the soft palate. After premedication with



<u>Figure 2</u>. Appearance of engorged tongue in the same patient on the 1st postoperative day. Note tremendous submental edema leading to protrusion of the tongue out of the oral cavity.

secobarbital 40 mg, morphine 1 mg and atropine 0.2 mg, general anesthesia was induced with nitrous oxide, oxygen and halothane by mask, and maintained using an endotracheal tube secured with a silk suture to the tongue. An intravenous catheter was placed in the left hand.

A total of 4 ml lidocaine 0.25% with epinephrine 1:400,000 was injected into the palate by the surgeon. A Dingman gag was used for retraction during the Veau-Wardill palatorrhaphy with intravelar veloplasty. Total blood loss was estimated at 100 ml and a total of 550 ml crystalloid was infused during the 4 hour and 45 minute procedure. When the patient was fully awake, the trachea was extubated in the operating room uneventfully with a satisfactory airway.

The patient developed massive, progressive edema isolated to the tongue and suprahyoid neck over the next 2 hours, compromising her airway to the extent that she could breathe only in the prone position. The tongue filled the oral cavity, with marked anterior protrusion (Fig. 1). The rigid engorgement of the tongue made oral reintubation extremely difficult, but this was eventually accomplished after multiple laryngoscopies. Lung fields were clear to auscultation immediately after intubation. The course in the pediatric intensive care unit over the next 36 hours was characterized by progressive macroglossia despite high-dose dexamethasone administration (Fig. 2). A pulmonary infiltrate identified on a chest radiograph and persistent fever were thought to be secondary to aspiration, necessitating antibiotic therapy. Peripheral hyperalimentation was also started on the 2nd postoperative day.

Although macroglossia had receded by the 5th postoperative day, visualization of the posterior

pharynx by laryngoscopy was still extremely difficult because of the severe lingual engorgement.

The following day, the endotracheal tube was dislodged when the patient moved vigorously. She was able to maintain an adequate airway without the endotracheal tube. Residual lingual edema resolved over the next week and she was discharged home on the 12th postoperative day.

Discussion

Development of postoperative macroglossia after cleft palate repair is an unusual complication that may lead to complete airway obstruction, necessitating immediate reintubation. In the cases we describe, distorted laryngeal landmarks and associated soft tissue edema made laryngoscopy extremely difficult. In addition, both patients developed aspiration pneumonia in the immediate postoperative period.

Several possibilities exist as to the etiology of macroglossia after cleft palate repair. Excessive pressure exerted by surgical retractors may cause glossal hematomas even in brief surgical procedures such as tonsillectomy. The Dingman mouth gag used in the cases described is a bladed ring retractor that holds the mouth open by exerting pressure on the tongue and alveolar ridge. Pressure associated with an excessively opened Dingman gag for a prolonged period of time can cause necrosis of tongue muscle, venous stasis and lymphedema. The glossal injury may be exacerbated by an extreme Trendelenburg position, which compounds venous stasis and lymphedema by gravitational fluid shifts.

The phenomenon of erectile tongue is well described in mammals (4) and has been suggested as an etiology in lymphangioendotheliomatosis macroglossia (5). The erectile activity is a result of cavernous tissue being acted upon by longitudinal muscle contraction, which in turn results in vascular expansion. This condition may present in the injured tongue.

The tongue is a highly vascular organ with muscles that are attached primarily to the hyoid bone. Figures 1 and 2 demonstrate the massive suprahyoid edema in the neck, a result of transudation of fluid and hemorrhage into the base of the tongue. This edema of the suprahyoid and submental region causes the floor of the mouth and anterior tongue to protrude. The weepy, cystic area on the undersurface of the tongue, characteristic of the lymphatic stasis seen in glossal lymphangioma (6), is also demonstrated.

One could speculate that these two infants may have had asymptomatic lymphangiomas or residual congenital lymphatic tissue rests, either of which may rapidly expand with injury or infection. Lymphagiomas develop embryologically from lymphatic tissue rests derived from the primitive jugular sac that become sequestered in the fetal tongue (7). Theoretically, noninvoluted lymphatic rests may persist in infants and provide a potential for glossal edema. Because lymphangioma spaces may interconnect, gravitational dependency as in Trendelenburg position may result in glossal and submental lymphedema.

Besides the immediate life-threatening complication of upper airway obstruction secondary to the massively enlarged tongue, both our patients experienced the additional complication of aspiration pneumonia that further prolonged their postoperative course. It is unclear whether this aspiration resulted from the loss of airway protection usually provided by a normally functioning base of the tongue and larynx, from multiple intubations, or from an air leak around the small endotracheal tube ultimately placed.

In conclusion, we present two cases of severe macroglossia after cleft palate repair in infants. Multiple anatomic and iatrogenic factors may play a role in the development of lingual and suprahyoid edema that may not be anticipated based on the findings of the preoperative examination and intraoperative course. Insidious and progressive airway obstruction may occur in the recovery room, and establishment of a patent airway or reintubation may be extremely difficult, if not impossible. Multiple attempts at tracheal intubation can disrupt the surgical repair and result in hemorrhage, compounding a potentially disastrous situation.

It is strongly recommended that the entire oropharyngeal cavity including the tongue and surrounding soft tissue be examined at the completion of cleft palate repairs before the endotracheal tube is removed. If any signs of lingual or suprahyoid edema exist, the endotracheal tube should be left in place and the patient carefully observed in the recovery room. Progressive edema necessitates prolonged intubation in the intensive care unit to ensure airway patency.

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Cardiopulmonary Bypass and Myocardial Protection: Management Problems in Cardiac Surgical Patients with Cold Autoimmune Disease

James V. Park, MD, and Carey I. Weiss, MD

Key Words: HYPOTHERMIA—cold autoimmune disease. SURGERY, CARDIOVASCULAR—cold autoimmune disease. IMMUNE RESPONSES—cold autoimmune disease.

Cold autoimmune diseases present significant problems in the management of cardiopulmonary bypass and myocardial protection in cardiac surgical patients. The cold autoimmune diseases can be classified into four types (Table 1), each with a variety of possible sequelae. Of the four types, cold hemagglutinin disease is characterized by IgM autoantibodies directed against the "I" antigen present on all red blood cells (1-6). With high titers, these pathologic autoantibodies may react even at physiologic temperatures (high thermal amplitude). Often their reaction is bithermic with hemagglutination at low temperatures and complement fixation and resultant hemolysis as normothermia is approached (1-4,7-10). Systemic hypothermia, routinely employed during cardiopulmonary bypass, can activate this system and possibly cause massive hemagglutination, microvascular thrombosis, or hemolysis. Cold cardioplegia may cause intracoronary hemagglutination with inadequate distribution of cardioplegic solutions, thrombosis, ischemia, or infarction (11-18). This case report illustrates one management plan, and a review of the literature reveals four additional techniques. These are compared and contrasted so that by considering the patient's pathophysiology and proposed procedure, the most appropriate management plan can be chosen.

Case Report

A 60-year-old man scheduled for coronary artery bypass graft surgery had a high titer cold agglutinin discovered in routine blood screening during hospitalization for a previous uncomplicated myocardial infarction. Two months before admission, an uneventful cardiac catheterization showed 90% obstruction of the left main coronary artery with significant additional disease in the left anterior descending, circumflex, and right coronary arteries. On the ventriculogram there was diffuse left ventricular hypokinesis with normal left ventricular end diastolic pressure. Despite recommendations to the contrary the patient chose medical management. In 2 weeks, the patient was readmitted after a second myocardial infarction complicated by mild congestive heart failure. He then agreed to surgery. Hematologic investigation showed a direct Coombs test positive for C₃d, negative for IgM. The patient had a cold agglutinin titer at 4°C of 1/10,000 (normal 1/40) and 1/5000 at 20°C. Thermal amplitude and critical temperature were not determined. Hemoglobin, hematocrit, serum bilirubin levels, urinalysis, and peripheral blood smear were normal. The patient had cardiomegaly, sinus bradycardia, normal levels of serum electrolytes, and a bleeding time of 9 minutes.

One day before surgery, plasmapheresis with six units of fresh frozen plasma replacement produced an eight-fold reduction in titers. After premedication with morphine 12 mg, and scopolamine 0.4 mg, IV, arterial, central venous, and pulmonary artery catheters were inserted while the patient was awake in a warm operating room. A warming blanket and warm IV fluids were utilized. Anesthesia was induced with fentanyl, and pancuronium was used for muscle relaxation. Body temperature (esophageal and extracorporeal venous return) was maintained above 35.5°C throughout the procedure. After heparinization, coronary artery bypass grafting was performed

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Table 1. Cold Autoimmune Diseases

Disease	Associate condition	Critical temperature* (°C)	References	Thermal amplitude* (°C)	Cold exposure
Cold hemagglutinin disease	None	(15–32)	1,2,3,4,9, and 10	(4–32) (≤ 31)	Acrocyanosis, hemolysis, Raynaud's phenomenon
Paroxysmal cold hemoglobinuria	Syphilis	(10– 15) (≤ 20)	1,19 19	$(4-15)$ (≤ 20)	Hemoglobinuria, hemolysis, jaundice, renal failure
Cryoglobulinemia	Macroglobulinemia	(17–33)	20,21	(0-33)	Hyperviscosity, immune complex nephritis, purpura arthralgas, vasculitis
Acquired cold autoimmune disease	Mycoplasma, infectious mononucleosis, mumps, leukemia, lymphoma	(4–6) (4–25)	1,2 4,8	(0–6) (≤ 25)	Acrocyanosis, purpura, hyperviscosity, hemolysis
Normal harmless cold autoagglutinins	None	$(4-10) (4-20) (10-15, \leq 20)$	1,19 3 4	(0-10) (0-20) $(0-15, \le 20)$	No reaction in vivo

^{*}Based on ranges reported from clinical and laboratory studies referenced.

during a 72-minute normothermic cardiopulmonary bypass at 36–7°C. Five distal saphenous vein anastamoses were placed using ischemic cross-clamp times of 14 and 9 minutes, with time for reperfusion in between. No ventricular fibrillation occurred.

Nitroprusside and nitroglycerine was started as cardiopulmonary bypass was terminated, and heparin was reversed with protamine. Six units of pooled platelets and two units of fresh frozen plasma were also administered. The hematocrit and hemoglobin levels, a peripheral blood smear, urinalysis, and plasma free hemoglobin and bilirubin levels were checked every 12 hours and remained in the normal range. No acrocyanosis or Raynaud's phenomenon developed. The postoperative course was unremarkable. No hemolysis, hemagglutination, myocardial infarction, or organ damage occurred.

Review

Thirteen cases of cardiac surgery in patients with cold hemagglutinin disease were reported between 1968 and 1985 (Table 2). In all patients with a known agglutinin the systemic temperature was maintained above the thermal reactivity of the cold antibody. Techniques of myocardial preservation included: 1) cold crystalloid cardioplegia; 2) plasma exchange; 3) normothermic ischemic arrest; 4) warm crystalloid cardioplegia washout followed by cold cardioplegia; and 5) warm blood-potassium cardioplegia. Normothermic cardiopulmonary bypass with ischemic arrest was successfully used in two of three cases, both

involving surgery for left ventricular aneurysm (17). The present case is the first reported using ischemic arrest for coronary artery bypass grafting in a patient with cold autoimmune disease.

Routine cold cardioplegia has been used in three previous cases of cold agglutinin disease (14,18,19). Agglutinates were found in the right atrium in two of these cases (14,18) and enzymatic evidence of myocardial infarction was reported in one of the three cases. In a fourth case (11), an aortic valve replacement was performed using 2 hours and 40 minutes of cardiopulmonary bypass at 29°C. Perioperative hemolysis requiring 17 units of whole blood prompted an investigation that revealed an agglutinin with a thermal amplitude to 22°C. The report does not mention use of a cardioplegic solution.

Plasma exchange has been used in 2 of the 13 cases. A documented ten-fold reduction in cold hemagglutinin titer occurred in one patient who received 19 units of whole blood perioperatively; the cause of the blood loss, body temperature, and duration of cardiopulmonary bypass were, however, unspecified, and there was no mention of myocardial protection. Our patient with left main coronary artery disease had an eight-fold reduction in cold agglutinin titer after plasmapheresis.

Four of the 13 patients (Table 2) had the heart isolated from the systemic circulation using bicaval cannulation with tourniquets, left ventricular venting, and a right atrial sump to visually confirm myocardial washout, with normothermic crystalloid cardioplegia infused into the aortic root after cross-

Table 2. Summary of the 13 Cases

Technique used	Number of cases	References	Complications	Advantages	Disadvantages
Cold cardioplegia	4	11* 14 18 19	Hemolysis requiring 17 units whole blood transfusion (11)	No increase in cost or time	Risk of agglutination, nonuniform cardioplegic distribution, and hemolysis
Plasma exchange	2	22† present‡	19 units whole blood transfusion (22)	Reduction of agglutinin titer; reduces risk of agglutination	Expensive, risks of hepatitis and abnormal hemostasis subjects patient with coronary artery disease to significant volume shifts
Warm ischemic arrest	3	17 present	None	No increase in cost or time; reduced risk of agglutination	Lacking presumed advantages of myocardial protection (perhaps best reserved for short procedures)
Warm crystalloid cardioplegia washout, cold crystalloid cardioplegia	4	14 16 23	Anterior myocardial infarction (14)	Allows repeated cold cardioplegia for myocardial protection; reduced risk of agglutination	Technically more complex and time consuming, delays cold cardioplegic protection to myocardium, risk of agglutination due to noncoronary collateral flow
Warm blood/ potassium cardioplegia	1	5	None	No increase in cost or time; reduced risk of agglutination	Lacks myocardial protection provided by hypothermia

^{*}No mention of cardioplegic use where an unknown cold agglutinin lead to hemolysis; reported here because 29°C cardiopulmonary bypass was used. †No mention of cardioplegic use.

‡Present case fits two categories, thus the total number of cases adds up to 14.

clamp. Cold cardioplegia immediately followed and all right atrial fluid was discarded. One patient had ECG and enzymatic evidence of anterior myocardial infarction (14). A cross-clamp time of 42 minutes was reported in one of the four cases using this technique (16).

Warm potassium-blood cardioplegia has been used without complication with a cross-clamp time of 42 minutes. The duration of bypass was not mentioned but the patient was kept 8°C above the critical temperature (20°C) of the hemagglutinin. Reactivity of the cold agglutinin decreased during cardiopulmonary bypass, perhaps because of hemodilution.

Discussion

Open-heart surgery routinely employs cardiopulmonary bypass and cardioplegia at various degrees of hypothermia. In patients with cold agglutinin disease these temperatures could cause hemolysis, inadequate cardioplegic distribution, myocardial infarction, renal or hepatic insufficiency, cerebral damage, or injury to other organs.

Complications of the various techniques are described in Table 2. None of the five techniques used to avoid problems during open-heart surgery in pa-

tients with cold autoimmune disease is clearly superior. Hemolysis occurs in all patients during cardiopulmonary bypass, especially with rewarming. There was no protection from agglutination afforded by heparin (24), nor by hemodilution. To a large degree, hemolysis during cardiopulmonary bypass may correlate more strongly with duration, flow rates, aortic cannula morphology, and the use of suction than with the presence of autoantibodies (25).

In formulating a management plan for cardiac surgical patients, several theoretical and practical aspects should be considered. Plasmapheresis should yield a substantial reduction (eight- to ten-fold) in agglutinin titers (22), but plasma exchange is costly and it subjects the cardiac patient to significant volume shifts plus the risks of infection and altered hemostasis. Ischemic arrest has been successfully used for coronary artery bypass. Noncoronary collateral flow provides some perfusion (26), but lacks the myocardial protection afforded by cold cardioplegia (27) and may best be reserved for shorter procedures. Warm crystalloid cardioplegic washout, though attractive for longer procedures, is technically more demanding. It requires isolation of the heart from the remaining circulation, which may be impossible due to noncoronary collateral flow (26). The warm cardio-

Table 3. Suggestions for Management

Preoperative

Routine 20°C crossmatch

Characterization of cold agglutinin, its thermal amplitude and critical temperature*

With acquired cold hemagglutinin disease, delay operation until cause is treated†

Intraoperative

Warm fluids, blood products, operating room and anesthetic gases

Limit transfusions; donor cells are not protected by C₃d. Use washed cells to limit complement transfusion

Maintain patient's systemic temperature above critical temperature of the autoantibody

Select myocardial protection using appropriate intraoperative management technique (Table 2)

With unsuspected agglutination: rapidly determine the critical temperature of the autoantibody and maintain the patient above it:

Postoperative

Follow intraoperatively and postoperatively for agglutination and hemolysis as evidenced by changes in: hematocrit, hemoglobin, peripheral blood smears, urinalysis, and plasma free hemoglobin and bilirubin levels, as well as acrocyanosis and Raynaud's phenomenon

Maintain patient's temperature in warm ICU room and warm all intravenous fluids and blood products

*Further screening is not clearly indicated (28).

tUsually malignancy or infection.

‡Highest waterbath temperature at which agglutination persists.

plegic washout also delays cold cardioplegic protec-

Although untoward effects of cardiopulmonary bypass in patients with cold agglutinin disease remain to be thoroughly documented, the hemolysis and theoretical damage that may occur warrant certain precautions. These are outlined in Table 3. This case report documents successful management of cardiopulmonary bypass in one patient with cold agglutinin disease.

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Delayed Respiratory Depression in a Child after Caudal Epidural Morphine

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL —morphine. ANALGESICS—morphine. ANALGESIA—postoperative. ANESTHESIA—pediatric.

The treatment of acute and chronic pain in adults with intrathecal or epidural narcotics is presently a widely accepted modality (1) and has been shown to be superior to conventional narcotic administration in several controlled studies (2–5). More recently, the use of epidural and intrathecal narcotics has been extended to children (6–8) and has also been demonstrated in this population to result in superior analgesia without an unacceptable frequency of side effects (9,10).

Respiratory depression, the most consequential side effect ascribed to spinal narcotics (11,12), is thought to result from rostral conduction of opioid dissolved in cerebrospinal fluid (CSF) to the brain stem with subsequent depression of medullary centers of respiration (1,13). Although well recognized as a risk in adult patients, it has not until now been reported in a child.

Case Report

A 2 1/2 year-old-boy was scheduled for one-stage repair of penile hypospadias. Past medical history and past surgical history were unremarkable, and there was no history of recent use of any medication. After discussion with the urologist it was decided to use postoperative caudal analgesia if an indwelling drain was to be left in the bladder, a decision which would be made intraoperatively. Options and risks

were discussed with the family, and tentative plans were made for caudal morphine to be administered for postoperative analgesia.

Anesthesia was induced with rectal thiamylal 22 mg/kg, after which halothane was administered by mask, an IV catheter was inserted, atropine 0.01 mg/kg administered, and the patient's trachea was intubated. General anesthesia was continued with halothane 0.7%-1.2% end-tidal concentration) in 100% O₂. No other medications were administered. At the conclusion of 4.5 hr of surgery, which included a urethroplasty and skin grafting with a pedicle flap, the patient was turned to the right lateral decubitus position, the hips were flexed, and a 20-gauge epidural catheter was inserted 2 cm into the caudal epidural space through an 18-gauge IV plastic cannula (Medicut). The introducing cannula was removed and the epidural catheter secured with a sterile dressing (Tegaderm). Inability to aspirate CSF and blood was confirmed, after which 4 ml 1% lidocaine (0.27 ml/kg) and 1.5 mg preservative-free morphine (Duramorph 0.1 mg/kg) were injected. The purpose of the lidocaine was to confirm proper placement of the epidural catheter by producing transient sacral-dermatome anesthesia. The patient was extubated while still anesthetized and allowed to awaken in the postanesthesia recovery room.

Fifteen minutes later the patient was awake and free of pain, and after another 30 minutes he was taken to the postoperative ward where he was monitored with continuous electrocardiography and a chest-wall impedance respiratory monitor set to alarm at a heart rate <70 beats/min or a respiratory rate <15 breaths/min. As is our practice, naloxone, oxygen, an oxygen-delivery device with mask, and suction were at the bedside. For the first 3 hours after the caudal injection the child was awake. Thirty minutes later the monitor alarm sounded. His nurse found him unarousable and cyanotic, with shallow respirations at a rate of 15 breaths/min and a heart rate of 108 beats/min. Oxygen was administered, followed by naloxone 10 μ g/kg, which resulted in

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improved respirations, resolution of cyanosis, and a return of consciousness. On arousal he complained of nasal pruritis. A capillary blood gas sample obtained after naloxone showed a pH of 7.3, Pco_2 44 mm Hg, and Po_2 56 mm Hg while breathing room air. Capnography was begun using nasal cannulae to sample tidal respirations. End-tidal Pco_2 was 42 mm Hg and respiratory rate 32 beats/min. An IV naloxone infusion of $10~\mu g \cdot kg^{-1} \cdot hr^{-1}$ was started.

Two hours later he became more somnolent and the end-tidal Pco_2 increased to 44 mm Hg. Intravenous naloxone (7 μ g/kg) was administered, and the naloxone infusion was increased to 14 μ g·kg⁻¹·hr⁻¹. Thereafter he remained awake or arousable and end-tidal CO_2 remained <40 mm Hg. The naloxone infusion was discontinued 16.5 hr after the caudal injection. The patient remained analgesic for a total of 14 hours after the caudal injection. Acetaminophen elixir with codeine was administered for subsequent complaints of pain. He was discharged home on the second postoperative day without residual effects.

Discussion

The delayed respiratory depressant effect of spinal opioids was first reported in humans shortly after the introduction of epidural and subarachnoid morphine into clinical practice (11). There followed sporadic reports of delayed respiratory depression in adults, but the risk remained largely undefined until the publication of a nationwide survey from Sweden, which reported 22 episodes of respiratory depression requiring therapy attributable to epidural morphine among approximately 6000-9000 patients treated with epidural morphine, or an overall incidence of three to four cases of respiratory depression per 1000 administrations (12). This study identified three risk factors for the development of delayed respiratory depression: 1) parenteral opiate administration in addition to epidural morphine (19 of 22 patients); 2) advanced age (10 of 22 patients were >70 years old); and 3) thoracic epidural injection (10 of 22 patients). Only two patients developed marked respiratory depression more than 6 hours after the administration of epidural morphine, suggesting that the period of greatest risk is the first 6 hours after the epidural narcotic injection.

Though the majority of patients treated with epidural morphine will not develop clinically significant respiratory depression, epidural morphine depresses ventilatory drive (airway occlusion pressure) and response to breathing CO₂ in the majority of patients for at least 6 hours after administration (13–16). This

roughly correlates with the more cephalad levels of segmental analgesia demonstrable after a single dose of epidural morphine, levels that may rise to as high as the trigeminal dermatomes by 9 hours following injection (13,16) in as many as half of patients (16). Recession of dermatomal analgesia occurred in these studies within 12 hours of injection. Bromage et al. (16) further observed that the occurrence of nausea and vomiting temporally correlated with the spread of hypalgesia to cervical dermatomes or above. Therefore, the risk of delayed respiratory depression may extend to 12 or more hours after injection, and the development of nausea and vomiting may mark those patients at particular risk.

Studies of adult patients have demonstrated that nonrespiratory side effects of epidural morphine are dose-dependent between 1 and 5 mg (17), but studies of the dose response of respiratory depression have been conflicting. Martin et al. (18) failed to demonstrate a dose-dependent effect of 0.5–8.0 mg of epidural morphine on end-tidal CO₂ or airway occlusion pressure during either normocapnia or hypercapnia. However, Rawal and Wattwil were able to demonstrate dose-dependent depression of minute ventilation and the response to breathing CO₂, the latter being evident after 10 mg but not after 2 or 4 mg of epidural morphine (19).

The collective clinical experience of anesthesiologists whose practice it is to administer epidural narcotics favors a starting dose of 3-5 mg of preservativefree morphine for postoperative analgesia in the typical adult. Against this background, the dose selected for this child, 1.5 mg, seems large. Selection of this dose was predicated on our assumption that larger doses would be needed for caudal than for lumbar epidural injection, based on our institution's prior experience with caudal morphine in children, which showed 0.1 mg/kg to be effective, associated with an acceptable incidence of urinary retention, nausea, and pruritis, and not associated with respiratory depression in our small study population (10). The published experience with epidural morphine in children <4 years old is very limited (8-10,14), and a dose response study to determine the safest effective dose of preservative-free morphine in small children remains to be published, though such a study is now in progress.

The work of Rawal and Wattwil (19) also importantly reveals that epidural morphine-induced reduction of minute ventilation is largely due to a reduction of tidal volume, and that respiratory rate is not significantly affected by spinal narcotic. This phenomenon bears on the selection of appropriate monitors for delayed respiratory depression because, as

this case illustrates, depression of respiratory rate, or frank apnea, may not always occur in dangerously depressed patients. Clinicians should therefore not rely solely on devices that merely count respiratory frequency. The capnograph provided minute-tominute reassurance of adequate minute ventilation in this child after his complication occurred and was treated. This device provides an early warning of hypoventilation, which will lead to either CO₂ retention and detectable elevation of end-tidal CO2 tension, or alternatively to significant artifactual depression of end-tidal CO₂ tension if tidal volume becomes inadequate, or if the airway becomes obstructed. Our subsequent experience has shown that capnography using nasal cannulae is reliable in small children, with an acceptable frequency of monitor false alarms due to disconnections or occlusions of the monitor cannula. Only in the presence of nasal obstruction due to an upper respiratory infection or adenoidal hypertrophy has capnography been unfruitful. Similarly, pulse oximetry will detect hypoventilation of such a degree as to produce arterial desaturation, the primary mechanism by which hypoventilation may produce harm to a patient.

Prevention of delayed respiratory depression and identification of patients at risk are more desirable goals than is detection by monitor of individuals once affected. Although posture has been demonstrated to be ineffective in decreasing respiratory depression after epidural morphine (20), prophylactic low-dose infusion of naloxone (5–10 μ g·kg⁻¹·hr⁻¹) has been shown in adults to prevent depression of the CO₂ response curve and to result in little or no diminution of analgesia (19,21). It is not yet known, however, if this treatment will diminish the occurrence of clinically significant respiratory depression or restore the CO₂ response curve to baseline values in young children.

In conclusion, delayed respiratory depression occurred in a 2 1/2-year-old child 3.5 hours after administration of 0.1 mg/kg preservative-free morphine in the caudal epidural space, in the absence of known risk factors. The child responded well to IV naloxone given by bolus injection followed by continuous IV infusion. The risk of delayed respiratory depression is present in children as in adults, though the magnitude of this risk and the period of maximum vulnerability are as yet undefined in children. This case illustrates that monitoring of respiratory frequency alone may not be adequate to detect delayed respiratory depression, and that end-tidal CO₂ monitoring, and/or oximetry, when available, may be more reliable early detectors of delayed respiratory depression after the administration of epidural morphine. This

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case further emphasizes the necessity to monitor respiratory parameters, and to have naloxone, suction, and an oxygen delivery device present at the bedside of children receiving spinal opioids, until they are well beyond the period of risk of delayed respiratory depression. A precautionary interval of 24 hours after the last dose of epidural morphine seems to be a reasonable period of observation (14).

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Helium-Induced Errors in Clinical Mass Spectrometry

E. Lynne Williams, FFARCS, and Don M. Benson, MD

Kev Words: MEASUREMENT TECHNIQUES mass spectrometry. GASES, NONANESTHETIC helium.

Mass spectrometry is used during clinical anesthesia to monitor inspired and exhaled respiratory and anesthetic gases (1,2). Although the mass spectrometer offers reliable information not previously available by monitoring pulmonary ventilation and anesthesia machine function (3,4), inadequate understanding of the spectrometer can lead to errors in the interpretation of the data reported by the machine. We present here two cases in which the introduction of helium into the inspired gas mixture resulted in erroneous data being reported by the Chemetron SARA II mass spectrometer (Allegheny International Medical Technology) in our operating room suite.

Case 1

A 71-year-old, 54-kg, 155-cm woman was scheduled for exploration of a large neck mass approximately 10 cm in diameter. The mass was located low in the neck just to the left of the trachea. Extension of the head provoked moderate respiratory difficulty, immediately relieved by returning the head to the neutral position. The trachea was not deviated on physical examination and showed no encroachment on the routine chest X-ray film.

by 3 mg d-tubocurarine. Anesthesia, induced with thiopental and followed by tracheal intubation facilitated by succinylcholine, was uneventful. Ventilation was controlled with a tidal volume of 550 ml at a rate of 10 breath/min. Inspired and expired gases were monitored with the mass spectrometer. Inspired oxygen concentration was also monitored with a Criti-

The patient was given 50 µg fentanyl IV followed kon Oxychek oxygen analyzer.

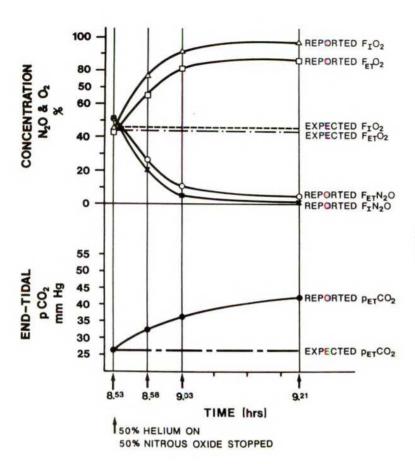
Nitrous oxide (50%) was administered with oxygen. Isoflurane was added into the inspired gas mixture to obtain a suitable level of anesthesia. After positioning, draping, and incision, the blood pressure decreased to unacceptably low levels. In an effort to maintain an Fio. of 50% without the potential myocardial depression of nitrous oxide, helium was introduced by a concentration of 50% and nitrous oxide was discontinued. Because the flow of a gas increases as its density decreases and the density of helium is less than that of nitrous oxide (approximately 1/10), it was also believed that a heliumoxygen mixture could enhance the gas flow past any tracheal obstruction that might occur during surgery (5). As helium replaced nitrous oxide in the system, the ventilatory pattern was left unchanged. The isoflurane concentration was varied as indicated by changes in blood pressure.

The inspired and end-tidal nitrous oxide levels recorded by the SARA monitor decreased from approximately 52 and 51% to 1 and 5%, respectively. Despite maintaining a gas flow of 2 L/min of both helium and oxygen (50% helium, 50% oxygen) the oxygen concentration recorded on the SARA monitor increased from 45.5% inspired and 43.8% end-tidal to 98% inspired and 88% end-tidal, respectively. With the tidal volume and respiratory frequency unchanged, the end-tidal carbon dioxide level reported by the SARA monitor increased from 26 to 42 mm Hg (Fig. 1). Because this phenomenon had been observed by us in a previous (unreported) case and a suitable explanation had been obtained then, blood gas tensions were not measured from the present patient. Surgery, anesthesia, and recovery were otherwise uneventful.

Case 2

A 47-year-old, 70-kg, 160-cm woman was anesthetized for cholecystectomy and cholangiogram. After induction with thiopental, tracheal intubation was facilitated with succinylcholine. An adequate anesthetic plane was achieved using isoflurane in a mix-

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<u>Figure 1</u>. Data reported by SARA monitor during administration of 50% helium and 50% oxygen compared with expected values.

ture of approximately 60% nitrous oxide and 40% oxygen. Inspired and expired gases were measured using the SARA clinical mass spectrometer. Inspired oxygen concentration was also measured using a Critikon Oxychek oxygen analyzer. Muscle relaxation was obtained with curare and ventilation was controlled with a tidal volume of 900 ml at nine breaths /min.

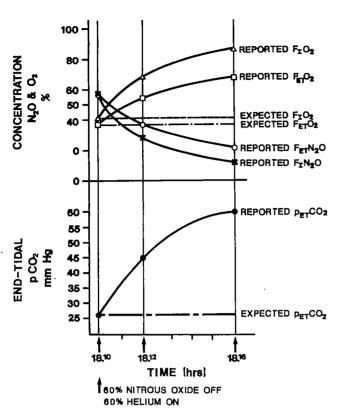
Shortly after surgery started, in an effort to minimize bowel distension, nitrous oxide was replaced with helium because the solubility of helium in blood is low: the blood gas partition coefficient of helium is about 1/40 that of nitrous oxide and 1/2 that of nitrogen. No other changes were made in the ventilation pattern or inspired gas concentrations. However, the mass spectrometer monitor indicated (Fig. 2) near-doubling of the inspired and end-tidal concentrations of oxygen and carbon dioxide 16 minutes after the substitution of 3 L/min of helium (FI_{HE}, approximately 60%) for 3 L/min of nitrous oxide.

Discussion

Helium has been used in anesthesia for several reasons: 1) Helium reduces the density of the inspired

gas mixture, thus increasing the flow rate through partially obstructed airways for a given driving pressure or degree of effort (6–11); 2) Replacing nitrous oxide with helium reduces the combustibility of the inspired gases, an important consideration for laser surgery of the airway; and, 3) helium can be used to reduce the inspired oxygen concentration when the use of nitrous oxide is undesirable, such as in patients with a closed air-containing space.

The clinical mass spectrometer analyzes gases using a combination of high vacuum and electromagnetic systems (1). Gases collected from the anesthesia breathing circuits are sampled serially by a computeroperated manifold system. A two-chamber high vacuum system widens the distance between individual gas sample molecules. The molecules are then ionized by an electron beam, accelerated in an electrostatic system, and directed through a powerful magnetic field. Because the trajectory of individual ions is a function of their mass-to-charge ratio, the path of specific agents can be identified. Ion counters are positioned to detect the number of "hits" caused by each substance. Thus, the identity and concentration of an unknown sample can be identified if there are plates in the appropriate positions for the substances



<u>Figure 2</u>. Data reported by SARA monitor during administration of 60% helium and 40% oxygen compared with expected values.

in that sample. An algorithm is used to calculate the concentrations of gases.

The SARA mass spectrometer assumes all gases in the system have been identified and, thus, the sum of all gases identified is estimated as 100% of the sample. The concentrations of gases in percentages are computed using this assumption and the Pco₂ in millimeters of mercury is calculated from the estimated contributory percentage. In contrast, the Perkin-Elmer MGA-1100 mass spectrometer displays partial pressures of gases and vapors (12,13).

The SARA mass spectrometer has no plate for measuring helium ion hits. Also, the molecular weight of helium (4) is so much lower than that of any of the measured gases that it would not impinge on any other plates. Thus, the contribution of helium to the total gas sample is ignored. In the cases presented, helium was added to the inspired mixture, but was not detected by the mass spectrometer. The system assumed all gases in the sample were detected and it calculated totals and percentages accordingly. Because 50% of the sample in the first case was undetected and 60% in the second, the values of the detected gases were displayed as approximately twice their actual values.

The error can be detected by the FI_{02} displayed by the mass spectrometer not correlating with the FI_{02} displayed by the separate system oxygen analyzer. (We keep a separate oxygen analyzer on each anesthesia machine for use when the mass spectrometer is inoperative for repair or maintenance.) Estimation of Paco₂ and Pao₂ would also demonstrate the inaccuracy of the SARA monitor.

It is important to be aware that the introduction of helium (or any other gas with no measuring plate in the SARA II mass spectrometer) will produce the cisplay of abnormal readings for the other measured gases. Otherwise treatment may be given to correct the erroneous readings. For example: hyperventilation may be used to reduce the displayed Petco2 to the normal range which would produce a hypocarbic, alkalotic patient with possible deleterious reductions in cerebral and coronary arterial flow.

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Changes in Sufentanil Pharmacokinetics Within the Neonatal Period

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Key Words: ANALGESICS—sufentanil. ANESTHESIA—pediatric

Decrused clearance rate and increased elimination half-life of the synthetic narcotics, sufentanil and fentanyl, have been reported in neonates when compared to older infants, children, and adults (1,2). The mechanisms for these pharmacokinetic differences noted in neonates as well as the time period at which mature drug metabolism occurs are unknown. We describe three infants who had sequential pharmacokinetic studies of sufentanil within the neonatal period where maturation of drug metabolism was observed.

Case 1

A 7-day-old, 3.0-kg neonate with a ventricular septal defect (VSD), patent ductus arteriosus (PDA), and coarctation of the aorta was anesthetized for coarctectomy and PDA ligation. At the time of surgery, the patient had congestive heart failure necessitating mechanical ventilation despite optimal medical management with dopamine, isoproterenol, prostaglandin E₁, and furosemide. Pertinent laboratory findings the day of surgery showed cardiomegaly on chest X-ray, BUN 10 mg%, creatinine 1.2 mg%, SGOT 24 U/L (normal reference range 5-35 U/L), SGPT 43 U/L (normal reference range 5-35 U/L), and total bilirubin 1.7 mg%. General anesthesia was induced and maintained with a single bolus of sufentanil 10 μ g/kg, pancuronium, and oxygen. Ventilation was controlled during the operative procedure and continued in the immediate postoperative period. The anesthetic and operative courses were uneventful. Aortic

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cross-clamp time was 23 minutes and estimated blood loss was 15 ml.

The postoperative course was marked by the redevelopment of upper extremity hypertension, persistent congestive heart failure, and the development of left lung infarction diagnosed by ventilation/perfusion scanning. Repeat cardiac catheterization revealed recoarctation of the aorta, a large VSD with left to right shunting, systemic pulmonary artery pressure, elevated left ventricular (LV) end-diastolic pressure, and total occlusion of the left pulmonary artery. Because of persistent coarctation and congestive heart failure (CHF) as well as persistent pneumonitis due to the pulmonary infarction, the patient presented for coarctation repair and left lung pneumonectomy at 28 days of age. At the time of surgery the patient required mechanical ventilation for respiratory failure, was receiving hyperalimentation for nutritional support, and anticongestive therapy consisting of digoxin, furosemide, and sodium nitroprusside. Pertinent laboratory findings at this time included persistent cardiomegaly on chest radiograph, BUN 26 mg%, creatinine 1.2 mg%, SGOT 25 U/L, SGPt 18 U/L, and total bilirubin 1.3 mg%. Anesthesia was induced and maintained with a single bolus of sufentanil 10 μg/kg, pancuronium, oxygen, and controlled ventilation similar to the first operative procedure. The anesthetic and operative courses were unremarkable, with a cross-clamp time of 25 minutes and an estimated blood loss of 25 ml.

In the immediate postoperative period, the patient maintained stable hemodynamics and respiratory function, was weaned from inotropic support, and extubated on the 5th postoperative day. Over the next few days the patient developed increasing respiratory distress requiring reintubation, mechanical ventilation, and inotropic support with dopamine. The patient continued to have acute, intermittent decompensations consisting of severe hypoxemia, hypercarbia, and hypotension despite maximal medical management of presumed episodes of pulmonary artery hypertension. The patient had a cardiac arrest

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on the 8th postoperative day during a severe hypoxemic, hypotensive episode, and died. Autopsy showed pulmonary hypertensive vascular changes, pulmonary edema in the right lung, a VSD, hypertrophied myocardium, and no residual coarctation. The liver showed swollen hepatocytes due to passive congestion and cholestatic changes secondary to hyperalimentation. The kidneys showed only patchy areas of tubular epithelial necrosis.

Case 2

*

A 4-day-old, 3.1-kg neonate with Ebstein's anomaly (right ventricular, dysplasia and tricuspid regurgitation) and pulmonary atresia was anesthetized for a right modified Blalock-Taussig shunt. At the time of the procedure the patient had severe hypoxemia due to reduced pulmonary blood flow while receiving an infusion of prostaglandin E₁ for maintenance of PDA patency and significant congestive heart failure despite dopamine and furosemide therapy. Pertinent laboratory findings before surgery included cardiomegaly on chest radiograph, BUN 16 mg%, creatinine 0.6 mg%, SGOT 92 U/L, SGPT 38 U/L, and total bilirubin 6.5 mg%. General anesthesia was induced and maintained with a single bolus of sufentanil 10 μ g/kg, pancuronium, and oxygen. Ventilation was controlled during the operative procedure and continued in the immediate postoperative period. The anesthetic and operative courses were uneventful; estimated blood loss was 10-15 ml.

The postoperative course was marked by respiratory failure due to persistent congestive heart failure and right hemidiaphragm paralysis occurring at the time of the initial surgery, requiring mechanical ventilation. Because of the paradoxical motion of the right diaphragm during spontaneous breathing contributing to ventilatory dependency, the patient was scheduled for a diaphragmatic plication on the 20th day of age. At the time of surgery the patient was receiving digoxin, a dopamine infusion, and furosemide as anticongestive measures and a procainamide infusion for control of atrial tachyarrhythmias. Pertinent laboratory findings at this time showed increased cardiomegaly on chest radiograph, BUN 23 mg%, creatinine 0.6 mg%, SGOT 105 U/L, SGPT 42 U/L, and a total bilirubin of 1.1 mg%. Anesthesia was induced and maintained with a single bolus of sufentanil 10 μ g/kg, pancuronium, oxygen, and controlled ventilation in a manner similar to the first operative procedure. The anesthetic and operative courses were unremarkable, with a estimated blood loss fo 25 ml. The patient was extubated on the 3rd postoperative day and was discharged in satisfactory condition on the 10th postoperative day.

Case 3

A 2-day-old, 3.3-kg neonate with a univentricular heart and pulmonary atresia was anesthetized for a left Blalock-Taussig shunt because of systemic hypoxemia. At the time of surgery the patient was being ventilated and was receiving a dopamine infusion for inotropic support and prostaglandin E₁ to maintain PDA patency and pulmonary blood flow. Pertinent laboratory findings before surgery included cardiomegaly on chest X-ray, BUN 12 mg%, creatinine 0.6 mg%, SGOT 47 U/L, SGPT 30 U/L, and a total bilirubin of 10.9 mg%. General anesthesia was induced and maintained with a single bolus of sufentanil 10 µg/kg, pancuronium, and oxygen. Ventilation was controlled during the operative procedure and continued in the immediate postoperative period. The anesthetic and operative courses were uneventful, and estimated blood loss was 20 ml.

In the postoperative period the patient could not be weaned from the ventilator due to left lung atelectasis, subsequent bronchoscopy showing extrinsic compression of the left mainstem bronchus due to aberrant origin of the left pulmonary artery (PA). Because of respiratory failure and ventilatory dependency, the patient was scheduled for a left PA division procedure through a median sternotomy at 27 days of life. At the time of surgery, the patient was receiving dopamine, isoproterenol, and sodium nitroprusside for hemodynamic support to control congestive heart failure and blood pressure instability, and hyperalimentation for nutritional support. Pertinent laboratory findings demonstrated increased cardiomegaly on chest X-ray, BUN 26 mg%, creatinine 0.6 mg%, SGOT 42 U/L, SGPT 88 U/L, and a total bilirubin of 7.6 mg%. Anesthesia was induced and maintained with a single bolus of sufentanil 10 μ g/kg, pancuronium, oxygen, and controlled ventilation in a manner similar to the first operative procedure. The anesthetic and operative courses were unremarkable, with an estimated blood loss of 20 ml.

Bronchoscopy on the 3rd postoperative day showed significant improvement of the bronchial compression. However, the patient could not be weaned from the ventilator due to development of an intercurrent pneumonia and died on the 8th postoperative day during an episode of gram-negative sepsis. Autopsy showed a univentricular heart with a single atrium and single AV valve, as well as a patent left Blalock-Taussig shunt, significant hypertrophy of

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Table 1. Sufentanil Pharmacokinetics

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Case	T ₁ (min)	$T_{\downarrow\beta}$ (min)		Cl ¹ -min ⁻¹)	Vd_{ss} (L/kg ⁻¹)	K_{10} (min^{-1})	$K_{12} \pmod{min^{-1}}$	K_{21} (min ⁻¹)
1								
X Y	23.2	434	4	.3	2.6	0.011	0.215	0.190
Y	7.1	160	18	.8	3.2	0.023	0.213	0.148
2								
X	20.7	332	6	.7	2.9	0.026	0.354	0.118
X Y	10.5	242		.3	3.3	0.027	0.264	0.255
3								
X	17.7	1140	1	.7	2.7	0.0041	0.290	0.215
X Y	8.8	248	12	.9	3.6	0.083	0.794	0.308
	A	α	В	β	P	π	K ₃₁	K_{13}
Case	(ng/ml)	(min ⁻¹)	(ng/ml)	(min^{-1})	(mg/ml)	(min ⁻¹)	(min ⁻¹)	(min^{-1})
1								
X Y	1.26	0.096	1.81	0.0016	9.99	0.623	0.045	0.200
Y	2.88	0.033	1.95	0 0048	7.47	0.395	0.016	0.027
2								
X	2.02	0.029	1.36	0.0021	15.98	0.567	0.013	0.090
X Y	3.60	0.079	1.25	0.0028	9.10	0.614	0.019	0.129
3								
X	5.32	0.039	3.51	0.0006	15.48	0.547	0.015	0.061
Y	7.04	0.066	1.47	0.0027	70.00	1.00	0.009	0.173

Abbreviations: X; First pharmacokinetic study (0–7 days). Y; Repeat pharmacokinetic study (20–28 days). $T_{\frac{1}{4}\alpha}$, Slow distribution half-life; $T_{\frac{1}{2}\beta}$, elimination half-life; $T_{\frac{1}{2}\beta}$, elimination half-life; $T_{\frac{1}{2}\alpha}$, slope of slow distribution half-life; $T_{\frac{1}{2}\beta}$, intercept of elimination half-life; $T_{\frac{1}{2}\alpha}$, slope of fast distribution half-life; $T_{\frac{1}{2}\alpha}$, $T_{\frac{1}{2$

the myocardium, and moderate pulmonary congestion. Liver showed generalized enlargement and swelling of the hepatocytes, with vacuolar and cholestatic changes resulting from hyperalimentation. The kidneys demonstrated congestive changes of the parenchyma.

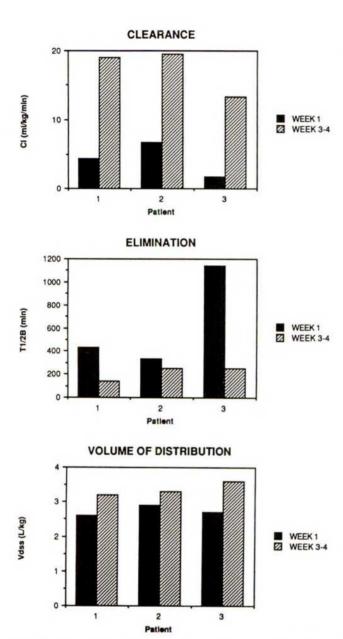
Pharmacokinetic Methodology and Results

As part of a standardized pharmacokinetic protocol approved by the Institutional Review Board, sufentanil was administered to each patient in the same bolus dose as part of the primary anesthetic for surgery during the first week of life. Each of the reported patients required a second major operation at 3 to 4 weeks of life, where sufentanil pharmacokinetic studies were repeated following the same protocol. During all studies arterial blood was sampled for measurement of plasma sufentanil concentrations before and 1, 2, 5, 9, 11, 15, 20, 25, 30, 35, 45, 55, 80, 100, 120, 180, 240, 300, 360, 480, 600, 900, and 1200 minutes after bolus infusion. Sufentanil plasma concentrations were determined in duplicate by radioimmunoassay (3) and the concentrations were fitted using a least squares, nonlinear regression to a threecompartment pharmacokinetic model (4). Table 1

summarizes the pharmacokinetic data in the three neonates. Using standard formulas (5), we determined slow distribution half-life $(t_{\frac{1}{2}\alpha})$, elimination half-life $(t_{\frac{1}{2}\beta})$, total plasma clearance (Cl), and the steady-state volume of distribution (Vd_{ss}) for each patient (6). In each patient there was an increase in Cl, decrease in $t_{\frac{1}{2}\beta}$, and increase in Vd_{ss} with advancing age during the neonatal period (Fig. 1). Clearance increased in Patient 1 by 441%, in Patient 2 by 291%, and in Patient 3 by 782%. Elimination half-life decreased in Patient 1 by 270%, in Patient 2 by 137%, and in Patient 3 by 460%.

Discussion

In neonates, important pharmacokinetic differences for the synthetic narcotics, fentanyl and sufentanil, have been reported when used as primary anesthetic agents when compared to older infants, children, and adults (1,2,7). Johnson et al. (8) first showed that fentanyl clearance is decreased in neonates compared to adult patients. Koehntop et al. (1) subsequently reported greater variability in clearance rates and increased elimination half-life of fentanyl in neonates. In a previous report we noted important age-associated decreased clearance and increased elimination half-life of sufentanil when used as a primary



<u>Figure 1</u>. Sequential pharmacokinetic analysis of sufentanil elimination $(T_{\downarrow\beta})$, clearance (CL), and volume of distribution (Vd_{ss}) in three neonatal patients.

anesthetic agent in neonates (2). Little is known about the mechanisms causing the variability and decreases in drug clearance observed in the neonatal age group in these studies. Furthermore, it is not known when mature drug elimination develops in newborns.

We report the first sequential pharmacokinetic studies of the same anesthetic agent within the first month of life in three patients, in whom age-associated maturation of drug elimination was observed. In all three patients the initial pharmacokinetic study was performed during the first week of life and repeated in each patient during reoperation

between 3 and 4 weeks of age. All patients had cardiovascular disease initially and had clinical and laboratory evidence of persistent congestive heart failure at reoperation. It is likely that congestive heart failure was also present at the first operation. Sequential analysis of hepatic and renal function (e.g., hepatic transaminases, total bilirubin, creatinine, BUN) showed mild and persistent abnormalities in liver and renal function. Autopsy in two of the cases revealed persistent congestive heart failure, passive congestion of the liver and renal parenchyma due to congestive heart failure. Despite these persistent pathophysiologic processes, i.e., congestive heart failure and hepatic dysfunction, the sequential pharmacokinetic studies in each patient revealed improved clearance and elimination of sufentanil. Because sufentanil is metabolized by oxidative N-dealkylation and subsequently cleared by the liver (9), the observed changes in clearance and elimination in our three patients were likely the result of changes in availability of sufentanil to the liver (hepatic blood flow) and/or changes in liver metabolism (maturation of microsomal enzyme activity).

Pelkonen et al. (9) demonstrated that microsomal enzyme activity is lower in human fetal than in human adult livers. These differences were related to maturational changes in organ development thought to occur in the neonatal period. Morselli et al. (10) reported a dramatic increase in the metabolic rate of drug degradation occurring during the first 15 days of life and speculated that the changes were due to the exposure of the neonatal liver to both inducing agents and redistribution of hepatic blood flow. The maturation of hepatic enzymatic activity would improve clearance and elimination due to improvements in drug degradation. Alternatively, redistribution of hepatic blood flow is known to occur in the neonatal period due to the closure of the ductus venosus, resulting in increases in hepatic blood flow (11,12). The latter would be expected to improve clearance because of increased availability of drug to the liver.

Comparing the neonatal pharmacokinetic data to our previous report, in which we examined various age *groups* in the pediatric population, in this study we observed similar changes in kinetics in the *same* patients advancing in age (Table 2)—that is, we observed a similar decrease in sufentanil clearance and increase in elimination half-life during the first week of life. The increase in clearance and decrease in elimination half-life by age 20–28 days is consistent with the pharmacokinetic data for the previously reported infant group (1 month to 2 years) (Table 2), giving direct evidence of the maturation of sufentanil

Table 2. Comparative Sufentanil Pharmacokinetic Values

Age	$T_{\frac{1}{2}\alpha}$ (min)	$T_{\frac{1}{2}\beta}$ (min)	$\begin{array}{c} Cl\\ (ml\cdot kg^{-1}\cdot min^{-1})\end{array}$	VD _{ss} (L/kg)
0-1 month* (n = 9)	23.4	737	6.7	4.15
1 month-2 years* $(n = 7)$	15.8	214	18.1	3.09
$2-12 \text{ years}^* (n = 7)$	19.6	140	16.9	2.73
12-16 years* (n = 5)	20.4	209	13.1	2.75
Neonatest (0-8 days)	20.5	635	4.2	2.7
Neonates† (20-28 days)	8.8	217	17.3	3.4

^{*}Pharmacokinetic values in the different age groups from a previous report (see Ref. 2).

tMean values of three neonates in present report.

kinetics in the same patients during the first month of life.

Our observation of improved sufentanil clearance and elimination in the neonatal period is most likely due to this known age-related maturation of the hepatic microsomal enzyme activity and/or agerelated redistribution of hepatic blood flow. Because clinical, laboratory, and autopsy evidence of persistent congestive heart failure, mild hepatic, and renal insufficiency was present in our patients during the neonatal period, disease-related improvements in sufentanil kinetics cannot be assumed. Although confounding variables such as a degree of congestive heart failure or hepatic blood flow were not quantitated, the persistence of cardiac, hepatic, and renal dysfunction throughout the neonatal period leads us to believe that age-related changes rather than disease-related changes were the primary factor improving sufentanil clearance and elimination. Alternatively, the exposure to other drugs during these patients' intensive therapy may have contributed to hepatic enzymatic induction and improved drug metabolism.

In conclusion, the present case reports offer the first evidence of age-related maturation of drug metabolism in the same patients with the same drug in the neonatal period. Our findings support the hypothesis of age-related maturation in hepatic enzyme activity and/or redistribution of hepatic blood flew with resultant improvement in sufentanil degracation. The variable rate of hepatic microsomal enzyme maturation as well as changes in redistribution of blood flow known to occur in the first weeks of life account for the variability observed in the use of

synthetic narcotics. The variability in clearance of sufentanil in the early neonatal period makes dosing of this drug and its duration of anesthetic response unpredictable. We believe this variability decreases during the neonatal period where sufentanil pharmacokinetics soon start to show pharmacokinetics seen in infants and children at approximately 1 month of age, allowing more predictable dose-responses for sufentanil at that time.

We thank Mrs. Ann Hogan for secretarial assistance in the preparation of this manuscript.

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Letters to the Editor

The Use of Nitrous Oxide Is Decreasing in Seattle

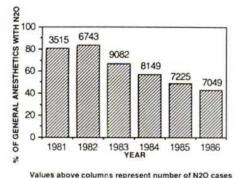
To the Editor:

Because of concern about the possible risk to operating room personnel, inhibition of methionine synthetase, increased nausea, expansion of gas-containing spaces, and other effects, the need for continued use of nitrous oxide has come under scrutiny (1). We wondered whether the controversy has led to a change in the use of the anesthetic in our clinical practice.

To answer the question, we determined the percentage of patients receiving general anesthesia with nitrous oxide at the University of Washington hospitals from 1981 through 1986, using a departmental data base (2).

Over the 5 years examined, the use of nitrous oxide decreased from a high of 84% in 1982 to 43% in 1986 (Fig. 1). Because there has been no formal change in departmental policy regarding the use of nitrous oxide and no major change in operative procedures or in our patient population, we attribute this decreased utilization to the increased publicity over possible adverse effects of the anesthetic. From these data, we were unable to determine whether this phenomenon is unique to our institutions, or whether it is representative of a national trend.

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<u>Figure 1</u>. The percentage of general anesthetics, utilizing nitrous oxide, administered at the University of Washington Hospitals from 1981–1986.

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Temporomandibular Joint Subluxation on Induction of Anesthesia

To the Editor:

Anesthesiologists are often concerned with the immobile temporomandibular joint secondary to rheumatoid arthritis, gout, trauma, or some other etiology (1). A recent article in this journal (2) reported an interesting problem of an abnormal temporomandibular joint resulting in inability to open the mouth for tracheal intubation under general anesthesia. This letter describes the opposite situation: hypermobility and subluxation of the temporomandibular joint associated with induction of anesthesia.

Anesthesia was induced in a 30-year-old woman having an emergency cesarean section with 5 mg/kg thiopental followed by 1.5 mg/kg succinylcholine IV. Preoperatively, it had been established that she had good mouth opening and neck flexion. Before full paralysis and before a jaw manipulation, the patient's mouth fell open spontar at usly with a yawn, and stayed in that position. Intubation of the larynx with an endotracheal tube was achieved easily and atraumatically. Surgery and delivery of a healthy baby followed uneventfully. On emergence from the anesthetic the patient was extubated in the left lateral position and allowed to breath oxygen via a face mask through her still open mouth. Over the next 30 minutes, she began to develop swelling and discomfort over the left temporomandibular joint and was unable to close her mouth. An urgent X-ray film was taken, confirming anterior subluxation of the mandibular head, which was easily reduced by an otolaryngologist, using intravenous diazepam for sedation. The patient's swelling and discomfort settled quickly and she regained full jaw mobility. Further inquiry revealed one previous episode, some years earlier, when the subluxation was associated with laughing.

This brief case report, although associated with no serious sequelae, should serve to remind anesthesiologists of this possibility in patients with previous subluxation. Dislocations of the temporomandibular joints have been

reported as a complication of fibreoptic bronchoscopy (3) and general anesthesia (4). This case was unusual, though, in that subluxation occurred before jaw thrust and intubation, either from a yawn after the IV induction or from masseter and temporalis muscle relaxation (these muscles being the normal temporomandibular joint stabilizers).

Most anesthesiologists would agree that in the course of a troublesome intubation attempt, with a vigorous jaw thrust and subsequent traction on the laryngoscope handle, temporary subluxation is possible even in patients with normal temporomandibular joints. Fortunately most reduce easily at the time, but we draw to the reader's attention the risks incumbent in not being aware that dislocation has occurred. Temporomandibular joint haematoma and subsequent intraarticular adhesion formation is a possibility, because the retrocondylar aspect of the joint is highly vascular. Displacement of the meniscus can occur and, rarely, auriculotemporal nerve damage from traumatic dislocation has been described (5) leading to joint laxiry. This could be embarrassing, professionally and medicolegally, if the joint was normal preoperatively.

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Control of Cocaine-Induced Hypertension with Labetalol

To the Editor:

Cocaine overdose evokes an overwhelming sympathetic stimulation of the cardiovascular system. Uncontrolled hypertension damages vascular endothelium, which may result in pulmonary and cerebral edema, hemorrhage, or infarct (1). The increased level of catecholamines may induce coronary artery spasm producing platelet aggregation (2). Autopsied heart tissue from cocaine fatalities has shown evidence of severe coronary obstructive lesions and areas of necrotic band scarring. Propranalol has been widely employed to control the hypertension induced by cocaine (3). However, a lethal hypertensive exacerbation has been attributed to unopposed alpha stimulation (4). Labetalol thus offers the advantage of both alpha- and beta-blockade.

To illustrate the profound cardiovascular crisis indued by cocaine, we report a 31-year-old man who ingested 20

gm cocaine. On arrival in the emergency room, his heart rate was 185 beats/min, his blood pressure 230/110 torr, his respiratory rate 30 breaths/min, and his axilary temperature 37.9°C. Within minutes the patient had a tonic-clonic seizure that was terminated with diazepam 10 mg IV. The airway was secured with an endotracheal tube. Electrocardiography showed a supraventricular tachycardia with mulifocal PVCs. A head CT scan revealed difuse cerebral edema. Labetalol, 20 mg IV bolus followed by an infusion at 160 mg/hr, proved effective in resolving this hyperdynamic cardiovascular state over a 4-hour period. Full recovery then ensued with the patient being discharged the following day.

Immediate medical response is essential in instituting measures to control the lethal complications of a cocaine overdose. A patient airway must be immediately secured and adequate oxygenation assured in the face of a hypermetabolic state. This case specifically demonstrates the use of labetalol in managing the cardiovascular crisis induced by cocaine.

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Silent Gene Recognition

To the Editor:

We read with interest the article by Smith et al. (1) That a patient with abnormal cholinesterase would respond as this one did could have been expected on the basis of other reports involving ester-type local anesthetics (2–4). The caution that they propose is absolutely correct. We believe, however, that the phenotype of this patient is different than that they propose. On the basis of a dibucaine number of 0 and a complete absence of cholinesterase activity, the diagnosis must be the extremely rare homozygous silent $(E_1^{s}E_1^{s})$ patient.

This situation was described by Liddell et al. (5) in 1962. In a heterozygotic patient carrying the silent gene, there would be cholinesterase activity and a dibucaine number totally dependent on the other gene (Table 1). In this particular instance, genotype may be identical to phenotype, but only family generational studies would be confirmatory.

Table 1. Pseudocholinesterase Variance

Genotype	Dibucaine number	Pseudocholin-esterase activity U/L		
E ₁ ^u E ₁ ^u	79–87	690-1560		
$E_1^{u}E_1^{s}$	78-86	329-870		
E, "E, "	55-72	433-1197		
$E_1^a E_1^a$	14-27	190-732		
$E_1^a E_1^s$	16-27	146-450		
$E_1^{\ s}E_1^{\ s}$	-	0-48		

Reprinted with permission from Viby Mogensen J. Cholinesterase and succinyl-choline. Copenhagen: Laegeforeningens Forlag, 1982;8.

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Epidural Air Bubbles and Frothy Syllogisms

To the Editor:

It is possible to imagine that a froth of air and fluid in the epidural space might impede transfer of local anesthetic across the meninges into the CSF, spinal roots, and cord (1). However, this concept has not been tested quantitatively. We do know that isolated bubbles are an inevitable consequence of the loss-of-resistance test (LORT) with air; therefore, we have advised that air be avoided when performing diagnostic peridurography (2), although countless epidural anaesthetics have been induced without inadequacies attributable to bubbles.

Dalens et al. (1) confirm that peridurography will always display isolated bubbles if air is employed for the LORT, but they use the association of bubbles with two cases of patchy epidural blockade as a major premise to conclude a cause and effect relation, and to impute bubbles as a universal bogey in all epidurals. This logic is flawed. Consider the two cases cited. Both had paravertebral tumors of unspecified, nature. The spinal canal was invaded and obstructed in one and, possibly in the other. An isotonic mixture of bupivacaine 0.5% and Iopamiron-200 (generic name, Iopamidol-200; contains 200 mg molecular iodine per ml; osmolality, 413 mOsm/kg at 37°C) was

injected in unspecified volumes and proportions. Iopamidol-200 is hyperosmolar (413 mOsm), and so an isotonic mixture may be estimated to contain six to seven parts of Iopamidol-200 and three to four parts of bupivacaine, with a final iodine concentration of 130–140 mgI/ml. The density of the peridurograms seems consistent with this concentration of iodine. The final concentration of bupivacaine would have been in the region of 0.15–0.2%, adequate for hypalgesia but inadequate for surgical anesthesia. Thus, patchy analgesia is entirely explicable on the pathologic and pharmacologic facts presented, without invoking more esoteric factors.

Heterodoxy is admissible when based on sound data and parsimonious logic, but in the words of William of Ockham "Non sunt multiplicanda entia praeter necessitatem"—"Don't complicate things unnecessarily."

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In Response:

We read with interest the comments of Dr. Bromage concerning our case report (1). We agree with his statement that cause and effect relations are virtually impossible to establish in humans because true experimental evaluations are not allowed, at least for ethical reasons (especially in children).

The problem of patchy epidural analgesia is irritating even if infrequent. Several mechanisms have been suggested to explain this: existence of an adhesive arachnoiditis, presence of an epidural median band and/or insufficient penetration of local anesthetics into the core of the roots (2,3). In our patients, the first two hypotheses are not tenable: arachnoiditis would have more probably occurred at the site of the tumor compression and the peridurograms are not consistent with either arachnoiditis or a median epidural band. With the latter hypothesis, painful gaps would have occurred in dermatomes supplied by large spinal nerves in the absence of additional factor(s) (such as epidural bubbles): this might have been expected for L3-S2 spinal nerves, as usually reported (2,3), but not for T12 or even L1, which are relatively thin spinal nerves (Fig. 1).

The injected solution consisted of 1 part 0.5% bupivacaine with 1/200,000 epinephrine (279 mOsm/ml) plus 0.66 part Iopamiron-200 (463 mOsm/ml). The final solution was 345–355 mOsm/ml with 0.30–0.31% bupivacaine. This concentration proved to be sufficient for completion of surgery in both patients cited in our paper and in many others of our personal series. The only problem encountered was related to the placement of a forceps on an area supplied by

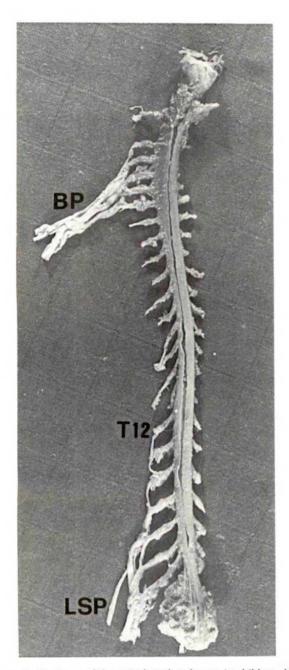


Figure 1. Anatomy of the spinal cord and roots in children. Note the relative size of spinal nerves at T-12 and L-3 levels. BP, brachial plexus; LSP, lumbosacral plexus.

the T12 or L1 spinal nerve, i.e., a few dermatomes below the upper limit of analgesia (Patient 1). Therefore, it is our impression that patchy anesthesia is not "entirely explicable" by the concentration of bupivacaine.

On the other hand, the peridurograms are consistent with the existence of epidural bubbles located close to the spinal roots and nerves supplying the unanesthetized dermatomes, while no bubbles in such a location could be found in other spinal segments (except at L3–L4 levels, as mentioned in Patient 2). This might have been fortuitous, but we found this unexpected association surprising enough to deserve reporting. Our objective was not to discourage the future use of the air detection technique by presenting it as a "universal bogey", but only to warn our colleagues of possible complications resulting from this technique.

Of course, thousands of uneventful anesthesia have been performed using the air-detection technique of the epidural space, but there also have been reports of specific complications including venous air embolism (4) and leakage of air into deep fascial planes of the back leading to cervical emphysema (5–7). We think that our observations suggest another potential complication of the air-detection technique: the possible role of epidural bubbles in producing or favoring patchy anesthesia. It would certainly be interesting if a (prospective) study could comparatively evaluate the frequency of unblocked segments after either air or fluid detection technique of the epidural space.

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Book Reviews

Cardiovascular Actions of Anesthetics and Drugs Used in Anesthesia Volume 2: Regional Blood Flow and Clinical Considerations

B. M. Altura, S. Halevy, eds., Basel, Switzerland: S. Karger, 1986, 294 pp, \$108.00.

This volume completes the twin monographs that were conceived to present, in a critical and state-of-the-art fashion, the effects of anesthetics on the cardiovascular system to "as large a biomedical readership as possible."

For this volume, the editors have again drawn on and, judging from the introduction and content, given free rein to an international roster of contributors. The result is a spectrum of quality, style, and adherence to the basic concept of the book.

The first part of the book picks up logically where Volume 1 left off and comprises chapters dealing with regional blood flow in various organ systems: the brain, the heart, the lungs, the splanchnic system, and the kidneys. The chapter on the pulmonary circulation ranks among the best reviews on this subject and, in a readable manner clearly and succinctly reviews the methodologic problems and interpretive pitfalls of the existing data, which are amply presented. The effects of anesthetics on the cerebral and the splanchnic circulations are reviewed, referenced, and interpreted in an exhaustive and scholarly fashion. On the other hand, the opening chapter entitled "Overview" and a separate chapter on liver circulation are examples of repetitions often inherent in a multiauthored text such as this, because no additional insights are expounded in these chapters. Without major editorial intervention, each repetition tends to reflect only the subset of literature surveyed and leads to conflicting conclusions.

Considering the editors' renown in microcirculation research, this reviewer is disappointed by the absence of discussion on the cellular mechanism of anesthetic effect on the vascular smooth muscle, the role of Ca²⁺ ion and antagonists, and the role of the endothelium.

The second part of the book, four chapters in all, is assigned to "highlight some clinical conditions which deserve particular attention." Herein the book begins to flounder. A straightforward review of the cardiovascular effect of anesthesia in children (hardly qualifying as a clinical condition) constitutes the first chapter. Two chapters that lack focus and consistency are devoted to shock

and trauma. The first chapter, entitled "Anesthetics and Shock: Practical and Basic Considerations," launches into a discussion of monitoring and a simplified rundown of various available anesthetics, but glosses over the fundamental aspects of shock and possible interaction with anesthetics. The second chapter, entitled "Influence and Use of Anesthetics on the Cardiovascular System During Shock and Trauma," is a most curious choice in such an advanced volume because it attempts to illustrate some clinical points using hypothetical case examples. It might be appropriate in an introductory text for medical students, except for the annoying and inaccurate writing, the pedantic stance, and some troubling suggestions. For example, how many anesthesiologists or intensivists would opt for a high spinal anesthetic as an afterload reducing agent in a trauma-shock patient, as proposed by the author? The last chapter, entitled "Hypotensive Anesthesia and Its Effects on the Cardiovascular System," is notable for the lack of discussion of the effect of induced hypotension on the circulation. Instead, it is a rather perfunctory description of the various pharmacologic agents available for induction of hypotension.

The well-read anesthesiologist and serious biomedical student will find in this volume little that is new nor enough critical writing to challenge their thoughts. A less experienced or learned trainee is apt to be confused by some of the presentations and suggestions. Nevertheless, the conception of these twin monographs was a commendable goal. This reviewer hopes that in a future edition, with more rigorous editorial effort, these two volumes can be consolidated into a single reference volume that will find a place in every medical library, and on every clinician's bookshelf.

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Handbook of Physiology, Section 3: The Respiratory System, Volume IV, Gas Exchange Leon E. Farhi, S. Marsh Tenney, eds., Bethesda, Maryland; American Physiological Society, 1987, 468 pp, \$165.00. The series of Handbooks of Physiology have earned widely deserved acclaim over the years as the sourcebooks for current, scholarly, and detailed treatments by recognized experts of the accumulating knowledge in physiology. This volume has maintained the tradition and is an outstanding collection of reviews on both theoretical aspects of the analysis of gas exchange and the functional performance of the pulmonary system as a gas exchanging organ.

The first 15 of the 20 chapters present the theoretical framework on which the physiology of pulmonary gas exchange has been developed. Although the topics may sound too familiar (i.e., ventilation-perfusion relationships, blood oxygen transport, carbon dioxide transport, and so on) or too dry (laws of physics pertaining to gas exchange or difference of gases), the presentations are neither. It is evident at once that the authors are emphasizing the new and important developments in their fields or have developed a fresh format to present a concept more clearly, which perhaps has not been appreciated before. The first two chapters are examples of the latter. A. B. Otis presents an overview of gas exchange as a sequence of conductance and pressure differences. The idea is not new in principle, but from the total picture some surprising insights emerge that will give the reader pause for thought. The topic of physics by R. H. Kellogg is developed entirely from the historic development of concepts, thereby revealing why we continue to use equations, units, and concepts that are paradoxical; the vignettes and asides are so nicely introduced as to bring the topics to life in an entertaining and valuable manner.

The details of gas exchange, including ventilation in the lung, both the convective and diffusive components, and the factors governing the exchange and carriage in blood are considered in consecutive chapters and each is a real contribution. Some of the highlights for this reviewer were as follows: The question of inhomogeneity of gas mixing in the alveolus has been an interesting theoretical question since it was suggested back in 1946. In a Chapter by J. Piiper and P. Scheid and in another by M. Hlastala, the theoretical and experimental basis and implications of this phenomena are discussed. While the theories have expanded considerably, the functional importance remains to be demonstrated. The discussion of ventilation-perfusion relationships by L. E. Farhi is as clear an explanation of the rational basis and technical consideration of the methods as is to be found. For those who have felt discouraged by this topic in the past, here is a concise, nonmathematical presentation by one who has been responsible for many of the developments in the field. There is even a discussion of the basis of diffusion hypoxia and second and third gas effects associated with anesthesia.

Another chapter that touches on anesthesia is a discussion by P. D. Wagner entitled "Peripheral Inert Gas Exchange." Behind the somewhat uninspiring title is a review of topics as diverse as anesthetic uptake in tissues, the principles of organ blood flow measurement, and factors influencing transcutaneous gas measurements. The chapter is a masterly synthesis of very diverse literature

into a comprehensive theory that is both creative and incisively written.

Many other chapters bear directly on the scientific basis of anesthetic practice. Gas exchange in body cavities, gas exchange in pregnancy, and gas exchange in the placenta are three such chapters. The discussion of gas exchange in the placenta is a thorough, informative and stimulating one that makes for difficult but satisfying reading.

These are the highlights of a volume that is well written, well illustrated and well edited. If there is one regret, it is that no specific chapter was devoted to gas exchange during anesthesia. However, the topic is fundamental to the specialty of anesthesia and this book can be recommended to all those wishing to pursue the physiologic basis for gas exchange at a depth beyond the usual textbook presentation.

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Medical Malpractice, A Preventive Approach W. O. Robertson, MD, Seattle: University of Washington Press, 1985, 212 pp, \$20.00.

Despite efforts at control, malpractice suits continue to be a major problem. This book presents a unique viewpoint on this issue; it is an outcome of the author's experience as head of the Washington State Medical Association (WSMA) Risk Management Program and as director of the Quality Assurance Program at Children's Orthopedic Hospital and Medical Center in Seattle. The author's basic premise is that physicians make errors, and that actual malpractice is the dominant explanation for the current malpractice problem. He notes that malpractice involves the full spectrum of medical practitioners, not just a few "bad" ones. The author also expresses the opinion that changes in the legal system, for example, elimination of contingency fees, or elimination of the jury, will not resolve the problem of physician error that results in patient injury. Rather, he suggests the profession must work together to reduce the incidence of error. Toward that goal Dr. Robertson systematically reviews major problems that result in malpractice suits. He proposes approaches to identifying these problems and techniques for resolving them. Chapters include a discussion of the doctor-patient relationship, informed consent, childbirth-related injuries, and problems with documentation.

There is little material in this book directly related to anesthesia. However, he discusses a review of malpractice experience in the State of Washington. The following were among the problems that led to malpractice suits or made a suit difficult to defend: problems with the airway, administration of the wrong drug or blood, anaphylactic reactions to rapid administration of antibiotics, the anesthesiologist leaving the room during the case, inadequate monitoring, and altered records.

The author strongly suggests that changes in practice will lead to a decreased incidence of law suits. Central to this proposal is the creation of review bodies in each hospital, anticipation and correction of problem areas, the institution of incident reports, and liaison committees at multiple levels to improve communication, particularly between physicians and nurses.

This book is particularly interesting in that it is written by a physician, yet does not blame the legal community, "litigious" patients, or a few bad doctors for malpractice problems. The book is brief and relatively easy reading. The author makes extensive and effective use of case studies to illustrate his points. The relatively brief section devoted to anesthesia might make this book less interesting in anesthesiologists, but the principles described apply to all medical specialties. The book would be particularly helpful to those involved in risk management. I suspect that a copy in one's hospital or medical school library would serve all potential readers quite well.

David S. Smith, MD, PhD Assistant Professor Department of Anesthesia Hospital of the University of Pennsylvania Philadelphia, PA 19104

Pharmacology and Physiology in Anesthetic Practice

R. K. Stoelting, Philadelphia: Lippincott, 1987, 859 pp, \$65.00.

This textbook, covering pharmacology and physiology is easy to read, detailed in the important areas, and achieves its aim. The author has made the study of pharmacology for anesthesiologists understandable, interesting, and as complete as the format will allow. The section on physiology is not as exhaustive but certainly is adequate if treated as an extensive summary.

The pharmacology of the cardiovascular and sympathetic nervous system is particularly well done. Chapters concerning prostaglandins, renin, and serotonin are welcome inclusions. Muscle relaxants and their antagonists are, as always, well explained by this author. The single writer approach has produced a clarity of style and selection of topics that are well suited to just what an anesthesiologist finds important. The intimate knowledge of the reference sources produces a uniformity of presentation and consistency of thought that is not always found in multiple author textbooks.

The introductory chapters are excellent and lead the reader directly into the maze of pharmacological principles that are now necessary to interpret the myriad drugs and effects found in anesthesiology. The selection of chapters and the topics found therein is adequate both for the inquisitive practitioner and for the reviewing resident who

earnestly needs solid information, both for his or her practice and for the inevitable examinations. Clearly, the writer is a knowledgeable and experienced teacher of anesthesiology who has been able to combine both attributes in his writing.

Many relevant clinical facts are used to produce emphasis and describe application. Personal opinion of the author is tempered throughout but, again, his extensive clinical experience enhances the reading experience. The textbook is a must for anesthesiologists of all levels. Because of its clarity it will be widely read and quoted, so all teachers should be acquainted with its contents.

Michael B. Howie, MD Associate Professor of Anesthesiology and Pharmacy The Ohio State University Hospitals Columbus, OH 43210

The Automated Anesthesia Record and Alarm Systems

Gravenstein, Newbower, Ream, Smith, eds., Stoneham, MA: Butterworth, 1987, 287 pp, \$38.95.

This is a great book! The authors and contributors are all acknowledged experts in their field and their accumulated clinical experience is presented in a group of papers from a symposium that concentrated on the most difficult area of computers in anesthesia. There are plenty of books on monitoring in anesthesia; this one focuses not on monitoring itself but the issue of what to do with the data acquired. In an era when new monitoring devices are appearing each year, the volume of data the anesthetist must review and record is increasing rapidly. Because most of these data are generated by machines, nearly all of this new data should be incorporated in the record. Because virtually all new instruments have a "computer" interface, the job of putting this data into the written anesthetic record should be trivial, right? Not so, and the reasons were apparent to anyone who has tried to create a system to accomplish this task.

What is needed is a clinical clerk (a diligent medical student would do) to observe and record the activity in the room and the numbers on all the monitor displays. Turning a computer into a clinical clerk is not currently possible, but if these authors have anything to say about it, the computerized clinical clerk is just around the corner. Readers of this book will get a good idea of how the machines of the next decade will perform.

The book has four sections comprising 24 papers, each independently written. An introductory paper begins each section and describes and contrasts the papers it contains. The writing throughout is refreshingly concise. Someone familiar with the field can read the entire work in a single day, although less experienced readers will want to read it more slowly.

The first section is also the weakest, and this is almost always the case for a section labeled "Philosophy." Mark Mitchell's chapter on human factors is excellent and should be required reading for all those who contemplate design of a new system.

The second section, "Systems and Technology," is the heart of the book. The best chapter is that by Frazier and Odom ("Spatial Organization of a Computer-Assisted Anesthetic Record"), which is clear and most informative. They trace several generations of computer-generated record in a single institution and describe how and, more important, why the successive versions took on all new formats. This chapter, more than any other, will be helpful to those wishing to computerize the generation of the record.

Part III, titled "Problems and Approaches," discusses some of the many issues surrounding alarms. Although much of the discussion is very general, Rampil's chapter on artifact is quite good, and Fukui's on artificial intelligence is novel and exciting.

The fourth section, "Acceptance," is interesting. Unfortunately there is a chapter on aircraft flight recorders and accident investigation that doesn't really belong in this volume. The comparison between flying a plane and piloting a patient through a surgical procedure is an old one, but not very apt. A plane is a mechanical device, relatively simple, easy to instrument, and exhaustively regulated and standardized. For the analogy to hold, one would have to take an aircraft with no sensors, install sensors and a recorder, fly it, land, and remove the sensors. Moreover the sensors would need to be universal—easily applied to any aircraft from a single-engine two-seater to a 747. This is clearly an idea that would not appeal to the pilots or passengers, and yet it is what we have to do in the case of anesthetic monitoring.

The paper by the lawyer is characteristically noncomittal. Perhaps a paper by a malpractice *plaintiff*'s attorney would have been more instructive.

What is missing from this book is any report from the industry that makes all the equipment. The monitoring business is very sophisticated and the new generation of machines incorporates soft keys, menus, elaborate alarms, and so on. In fact, the latest generation of monitors has already standardized many features of the display, including trend recording and artifact rejection. One wishes for a

review by representatives of Siemens, Marquette, Hewlett-Packard and Spacelabs!

In all, this book is very useful. Academic anesthesiologists and engineers will find it most useful. Practicing anesthesiologists will enjoy its style and especially the introductory papers.

It is a certainty that the automated anesthetic record is coming. It is equally certain that it will be different from anything presented here. This book gives us a view "through a glass darkly," which is well worth reviewing. Anyone serious about monitoring and record keeping will want to own a copy.

John S. McDonald, MD Professor and Chairman Department of Anesthesiology The Ohio State University Columbus, OH 43210

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Astrap P, Severinghaus JW. <u>The History of Blood Gases, Acids, and Bases</u>. Copenhagen Munksgaard, 1987, 331 pp, \$34.95.

Constant J. <u>Electrocardiography</u>, A <u>Complete Course</u>, 3rd Edition. Boston: Little, Brown, 1987, 640 pp, \$48.00.

Donegan JH. Mannual of Anesthesia for Emergency Surgery. New York: Churchill Livingstone, 1987, 403 pp, 529.00.

Harf A, Duroux P, Lemaire F, et al., eds. <u>Function Diaphragmatique Travail Respiratoire</u>, Paris: Expansion Scientifique Francaise, 1987, 251 pp, 545.00.

Hinds CJ. Intensive Care, A Concise Textbook. Philadelphia: Balliere Tindall, 1987, 378 pp, \$29.95.

Israel JS, DeKornfeld TJ. <u>Recovery Room Care</u>. Chicago: Year Book Medical Publishers, 1987, 355 pp, \$44.00.

Katz J, Renck H. <u>Handbook of Thoracoabdominal Nerve Block</u>. Orlando: Grune & Stratton, 1987, 196 pp, \$69.50.

Reves JG, Hall KD, eds. Common Problems in Cardiac Anesthesia. Chicago: Year Book Medical Publishers, 1987, 551 pp, \$46.95.

Roizen MF, ed. Anesthesia for Patients with Endocrine Disease. (Vol 5, No 2 of Anesthesiology Clinics of North America). Philadelphia: WB Saunders, 1987, 217 pp, \$25.95.

Stevens J, ed. <u>Preparation for Anaesthesia</u>. (Vol 4, No 3 in Clinics in Anaesthesiology Series). Philadelphia: WB Saunders, 1986, 353 pp, \$25.95.

Verderama M, ed. <u>CRC Handbook of CNS Agents and Local Anesthetics</u>. Boca Raton, Florida: CRC Press, 1986, 378 pp, \$150.00.

A Guide for Authors

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 Personal author(s) books and monographs Eisen HN. Immunology; an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406. 	 Consult the following sources for abbreviations: CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and 				
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PRECAUTIONS:

PRECAUTIONS:

Questil: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anapthylactoid reactions or estimal suggesting a greater risk of histamine release. In these patients, the recommended trittal Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses never one include.

Since Tractium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tractium than with other muscle

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug interactions: Drugs which may enhance neuromuscular blocking action of Tractium include: enflurane; Isoflurane; halothane; certain antiblotics, especially the eminoglycosides and polymyxins; lithium; magnesium saits; procainamide; and quinkline.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succ nylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tractium. Tractium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Inspairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated calls. A far weaker response was observed in the presence of metabolic activition at concentrations which also idlied over 80% of the treated cells.

Pregnancy: Teralogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teralogenic in rabbits, when given in doese up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relevants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Fractum (0.3 mg/kg) has been administered to 26 pregnant women during delivery by casarean section. No harmful effects were attributable to Tractium in any of the newborn infants, atthough small amounts of fractium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn Infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administrated. In patients receiving magnesium suitate, the reversal of neuromus cular blockade may be unsatisfactory and Tractium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been

ADVERSE REACTIONS

Cobserved in Centralied Clinical Studies: Tracefum produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of Hitle clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows in those patients given the recommended nitial dosage range of 10.31 to 0.50 mg/kg of Tractium, mean enterial pressure increased in 2.8% and decreased in 2.1% of patients withe the heart rate increased in 2.8% of these patients. At doses of > 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% and decrease in heart rate. At coses < 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increases in 1.6% and decreased in 0.8% of these nations.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: General: altergic reactions (anaphylactic or anaphylacticid) which, in rare instances, were sewere (e.g., cardiac arrest); Musculoskeletal: inadequate, prolonged block; Cardiovascular: hypotension, vasodilatation (flushing), tachycardia, bradycardia; Respiratory: dyspnee, bronchossem languagement Intercentation and unificate infection site reaction. spasm, laryngospasm; integumentary: rash, urticaria, injection site reaction

¹Payne J: Atracurlum, In Katz R (ed): Muscle Relaxants: Basic and Clinical Aspects. Orlando, Grune

Payne 3: Atracultum, In Katz R (sd): Muscle Relaxants: Basic and Clinical Aspects. Orlando, Grune & Stratton, 1964, p. 98.

*d'Holander A, Luyck C. Bravis L: Clinical evaluation of atracultum besylate requirement for a stable muscle releasation during surgery: Lack of age-related effects. Anasthesia 1983;59:237—240.

*Durvaklestin P, Saada J, Berger J., et al. Pharmacokinetics, pharmacodynamics and dose response relationships of paneuronium in control and elderly subjects. Anasthesia 1982;56:38—40.

*d'Holander A, Massaux F, Neve steen M: Age-dependent dose-response relationship of Org NC45 in anasthetized patients. Br J Anaesth 1982;54:653—657

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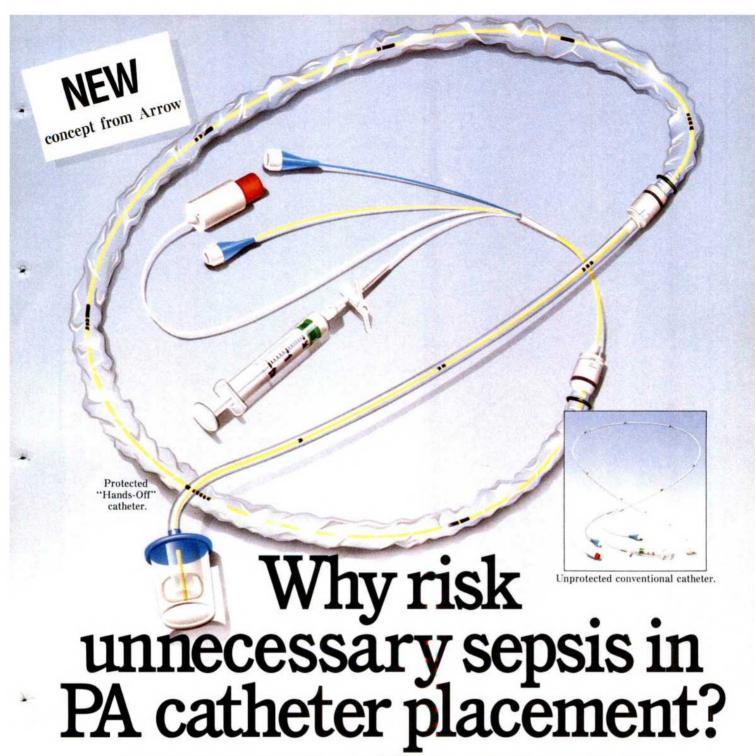
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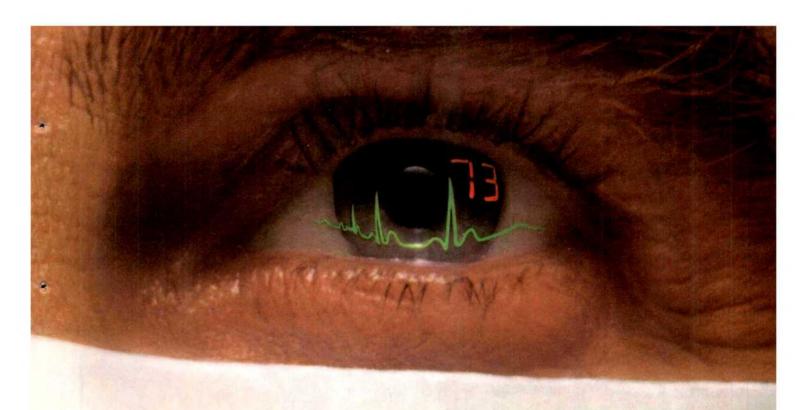
"...remarkably complete and pleasant."*.

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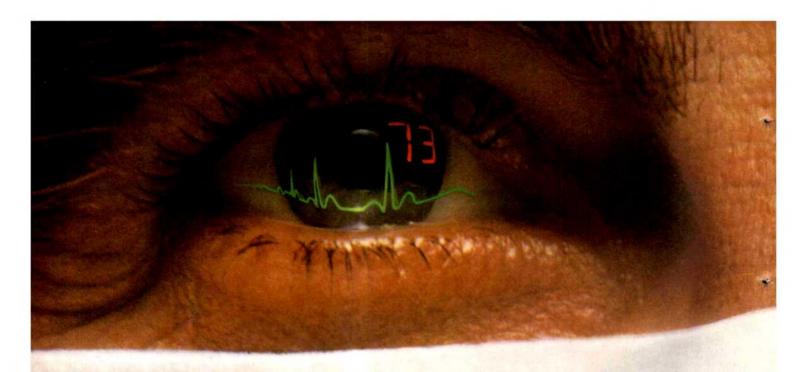
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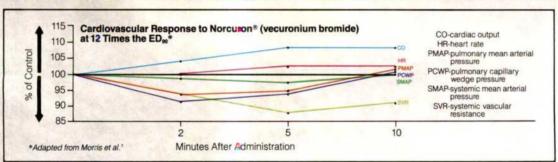
ideal for your patients, including those at risk.1-5



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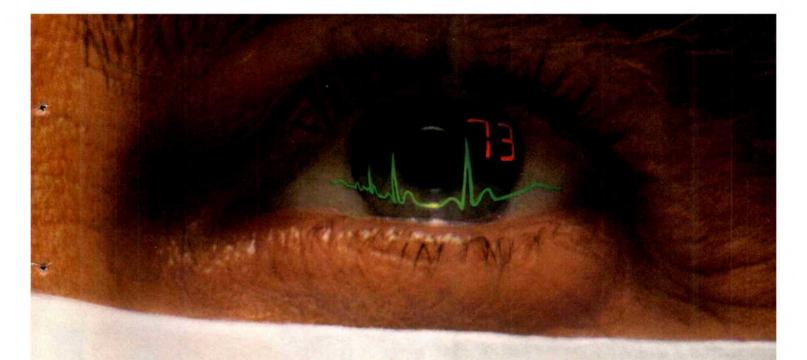
NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials. ¹⁴ In fact, even at 12 times effective doses, under halothane anesthesia, ¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



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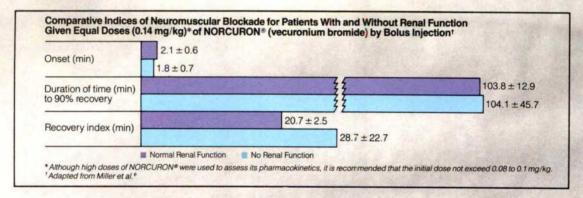
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range. §

Drug	Dose (mg/kg)	xED ₉₆	Histamine		Mean Arterial Pressure		Heart Rate
Tubocurarine	0.5	1	RIVER NO.	410	78	8	116
Metocurine	0.5†	2	212	Sill Saint	79		119
Atracurium	0.6†	3	192		80		108
Vecuronium	0.1	1.7	117	Williams		100	99
Vecuronium	0.2	3.5	87			99	102



Performance unaffected by renal function.6

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



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Norcuron[®] (vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al. The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1983, 58:438-440. 2. Durant NN. Norcuron®—a new nondepolarizing neuromuscular blocking agent. Semin Anesth 1982, 147-56.

3. Krieg N, Crul JF, Booj LH. Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. Br J Anesth 1980, 52:783-787.

4. Gallo JA, et al. Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. Anesthesiology 1984; 61: A63. 5. Basta SJ, et al. Vecuronium does not alter serum histamine within the clinical dose range. Anesthesiology 1983; 59: A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide). Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron* (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAF WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blicsking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidiny)) androstan-16-yi]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buttered cake of very line microscopic crystalline particles for intravenous injection only Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains cities acid, dibasic sodium phosphale, sodium hydroxide, and/or phosphoric acid to butter and adjust pH and mannitol to make isotonic. CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing reucornsucular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curaritum). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, exponential and pyridostigmine. Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to oneat of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The time to oneat of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The time to oneat of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The time to maximum neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to maximum neuromuscular blockade within 3 to 5 minutes of injection in most within a saveraged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg openerally produces first depression of twitch in approximately 1 minut

command our action of 25-30 minutes. If succinylcholine is used prior to Norcuron*, the administration of Norcuron* should be delayed until the patient starts recovering from succinylcholine-induced murromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron* has not been studied (see Drug interactions).

Repeated administration of maintenance doses of Norcuron* has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 10 8to 0.10 mg/kg (under balanced aneshesia, the first maintenance duses (suggested maintenance dose) to 100 to 0.05 mg/kg (see under balanced aneshesia, the first maintenance duses (suggested maintenance dose) to 100 to 0.05 mg/kg (see under balanced aneshesia).

The recovery index (time from 25% for 55% recovery) is approximately 15-25 minutes under balanced or halothania nesthesia. The recovery index (time from 25% for 55% recovery) is approximately 15-25 minutes under balanced or halothania nesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery index (time from 25% for 65% recovery) is approximately 15-25 minutes under balanced or halothania nesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery index (time from 25% for ecovery) is approximately 15-25 minutes under balanced or halothania recovery index (time from 25% recovery) is approximately 5-25 minutes under balanced or halothania recovery index (time from 25% recovery) is approximately 5-45 minutes in healthy suggest balance or approximate or approximate or approximate or approximate or approximate or approximately 4-45 minutes in healthy suggest balance or approximately and the formation of the format

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron* has no clinically significant effects or observed with anesthetic agents. Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactors commonly associated with histamine release are unlikely to occur. MINICATIONS AND USAGE. Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal intuitation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. CONTRAINDICATIONS: None known. WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY CR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILLAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION. ARTIFICIAL RESPIRATION, DXYGEN THERRY, AND REVERSAL AGANTS ARE INSECURITIES FOR INTUBATION. ARTIFICIAL RESPIRATION, DXYGEN THERRY, AND REVERSAL AGANTS ARE INSECURDED AND ARE FAMILLAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION. ARTIFICIAL RESPIRATION, DXYGEN THERRY, AND REVERSAL AGANTS ARE INSECURDED AND ARREST AND ARRE

should not be increased

should not be increased.

Hepatic Diseases: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron* metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS. USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MIDNITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking appents such as Nocuron®.

agents such as Notice of the Mark Mark drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capatile of triggering

matignant hyperthermia.

Norcuron* has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. Whis succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron* before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been explicated the children. sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (paneuronium, d-lubocurarine, melocurine, and gallamine) act in the same tashion as does Norcuron*, therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relearnts in the same patient.

relayants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesis a unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Artibiotics: Preneral/integeritoneal administration of high doses of certain antibiotics may intensify or produce neuro-muscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycomuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron* during surgery, unexpected prolongation of neuromuscular block should be considered a possibility of their Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animats (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to after neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade. cular blockade

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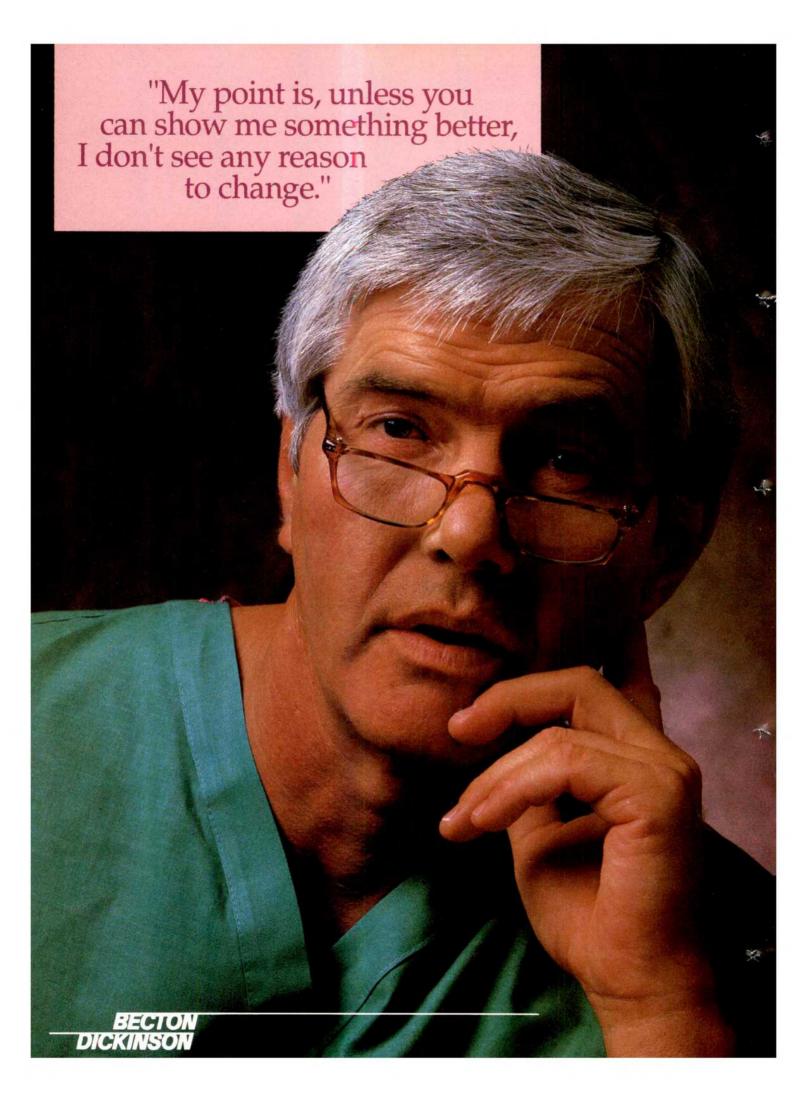
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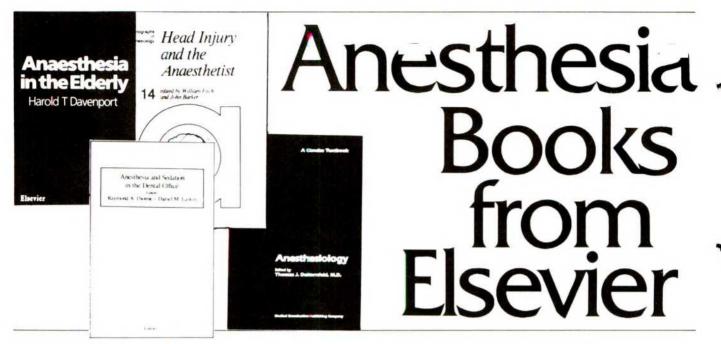
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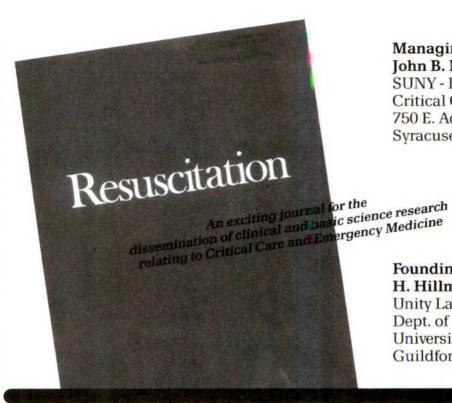
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- Ravin MB. Pyridostigmine as an antagonist of d-tubo-curanrine-induced and pancuronium-induced neuromus-cular blockade. Anesth Analg—Curr Res 54:317-321, 1975.



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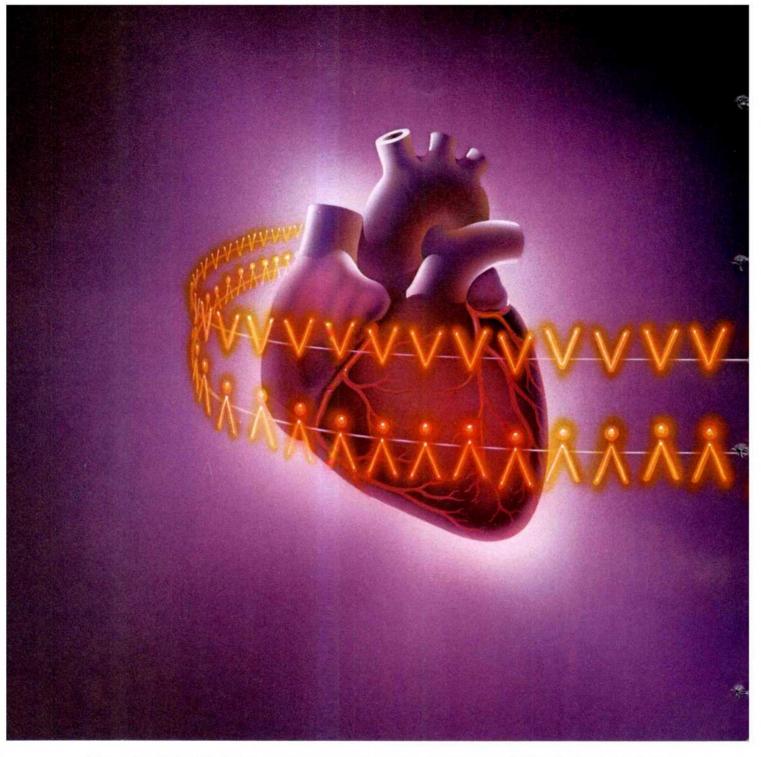
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DESCRIPTION: SUFENTA is a sterile, preservative free, aqueous solution containing suffernant citrate equivalent to $50~\mu g$ per ml of sufentanil base for intravenous injection. The solution has a pH range of $3.5 \cdot 6.0$.

INDICATIONS AND USAGE: SUFENTA (sufentanii citrate)is indicated: As an analgasic adjunct in the maintenance of balanced general anasthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures. Such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardiatand cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FUR MORE COMPLETE INFORMATION ON THE USE OF SUFFINIA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensilivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent-opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent

following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuro-muscular blocking agent when SUFENTA is used in rapidly administrated anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLLOGY). The hemodynamic effects of a particular muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid enalgesics can be reversed by opioid analognists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist actien, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CD₂ stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cerdiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries impaired Respiration. SUFENTA should be used with caution in patients with bulmonary disease, decreased respiratory drive and increase airway resistance. During anesthesia, this can b

THAT KEEPS PATIENTS ON TRACK

(sufentanil citrate) Injection

Predictable control for longer, more stressful procedures

PROVIDES smooth induction¹

BLUNTS hemodynamic response to intubation and surgical stimulation2

REDUCES need for vasoactive drugs in the intraoperative and postoperative periods1

RESULTS in lower postoperative morbidity after aortic surgery compared with isoflurane3

(in a randomized study comparing sufentanil and isoflurane)

CONVENIENT: Fewer ampoules to open

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames Salmonella upphimurium metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in coses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD $_{50}$ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinee pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of points are respiratory decreasion and ANYESE REALTIONS: The most common average reactions of opinions are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involv-ing 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: Cardiovascular: tachycardia, arrhythmia Gastrointestinal: nausea, vomiting Respiratory: apnea, postoperative respiratory depression, bronchospasm Dermatological: itching, erythema Central Nervous System: chills Miscellaneous: intrapperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanti citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdesage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARNACOLOGY) as with other potent opioid analgasics. However, no experiences of over-dosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/tg (see ANIMAL TOXICOLOGY for LD₅₀S in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidate to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or agnee. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respira-tion. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and SUFENTA should be determined on the t debilitated patients (see PRECAUTIONS).



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U.S Patent No. 3,998,834 January 1986, March 1986 © Janssen Pharmaceutica Inc. 1987

Anaquest

Enlon®

(edrophonium chloride injection, USP)

A rapid-acting neuromuscular reversal agent

From the developers of Ethrane (enflurane) and Forane (isoflurane)



60-second reversal of neuromuscular blockade

- Onset of reversal significantly faster than with neostigmine or pyridostigmine—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.^{1,2}
- Duration of reversal comparable to that of neostigmine—66 minutes versus 76 minutes for neostigmine. 1,2,*
- Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using twice the atropine dose (15 μg/kg).^{1,2}
- May be the preferred reversal agent for atracurium and vecuronium
 "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."
 - "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."

^{*}Note: When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

^{1.} Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Anaquest

Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethy. (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is

ENLON contains in each mL of sterile solution

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is acjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the mycneural

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, meto-curine atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having winary obstructions of mechanical type.

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vacotonic

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient abould be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug

may worsen the condition of these patients (see CVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown

Nursing Mothers: The safety of ENLON during lactation in humans has not been

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anti-cholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, incre Muscarine-like symptoms (nausea, vomtung, duarnea, sweating, increased proncinal and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia-should be avoided as tenacious secretions and bronchial plugs may form Should edrophonium chloride overdosage occur:

- 1. Maintain respiratory exchange.
- 2. Monitor cardiac function

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

nded adult intravenous injection for antagonism of neuromuscular

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions

Children:
Intravenous dose in children weighing up to 75 pounds:
Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is

Intravenous dose in children weighing above 75 pounds: Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis: The test dose of ENLON should follow one hour after oral intake of the drug being

used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized. Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs. ENLON (edrophonlum chloride injection, USP) Test in Crisis:

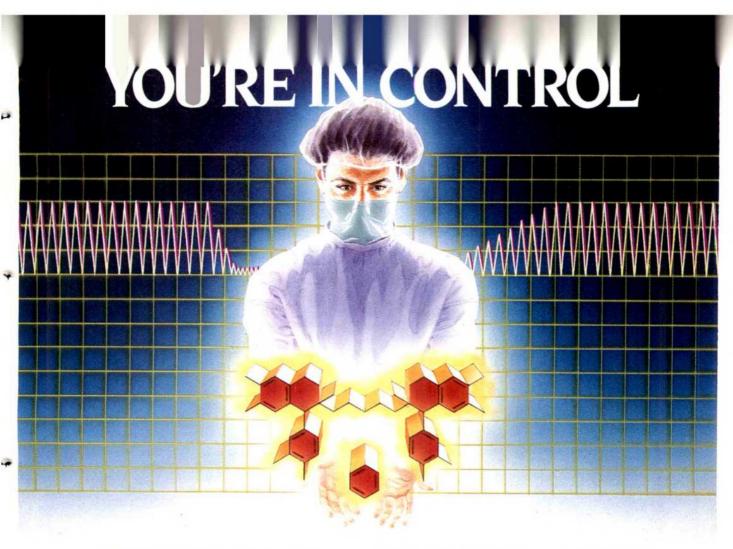
Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

avoid cardiac arrest and irreversible central nervous system damage. The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administrated. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

ENLON (edrophonium chloride injection, USP): NDC 10019-873-15 15 mL multidose vials

Revised 10-85

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TRACRIUM® (atracurium besylate)
Injection is meaningfully different from all other neuromuscular blockers. TRACRIUM is inactivated in plasma by two pathways, Hofmann elimination and ester hydrolysis, that act independently of liver or kidney function. This unique metabolism can result in *superior control* and makes possible:

■ More Predictable Dosing

The unique metabolism of TRACRIUM eliminates the need for age-related dosage adjustments. Valuable time is not lost making dosage calculations.

■ More Predictable Response

Repeated equipotent doses of TRACRIUM, administered at equal intervals, have no cumulative effect.²

Response is predictable, even with multiple injections or long periods of continuous infusion,³ allowing you additional time for patient monitoring.

■ More Predictable Recovery

With TRACRIUM, you can feel confident of a predictable conclusion to neuromuscular blockade. And your patients can be in the recovery room faster.

■ More Predictable, Superior Control

TRACRIUM is an excellent agent for administration by repeated bolus injection or continuous infusion. The lack of cumulative effects of TRACRIUM by infusion makes possible a smooth, steadylevel relaxation without the need for multiple maintenance bolus doses throughout a long procedure.

TRACRIUM® INJECTION

(atracurium besylate)

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, character-

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT, EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE. FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE

DO NOT GIVE TRACRILIM BY INTRAMUSCULAR ADMINISTRATION

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering fracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphyliadrolid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range. It will not counteract the bradycardia produced by mary anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome. or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis

The safety of Tracrium has not been established in patients with bronchial asthma

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins. lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered

The prior administration of succinylcholine does not enhance the duration, but guickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succirylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been

ADVERSE REACTIONS

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At does of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% and an increase in heart rate. At doese ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: General: allergic reactions (anaphylactic or anaphylacticid) which, in rare instances, were severe (e.g., cardiac arrest); Musculoskeletal: madequate, prolonged block; Cardiovascular: hypotension, vasodilatation (flushing), tachycardia, bradycardia; Respiratory: dyspnea, bronchospasm, laryngospasm; Integumentary: rash, urticaria, injection site reaction

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The MIDWEST ANESTHESIA CONFERENCE (MAC)

May 12th-14th, 1988 **Hvatt Regency Hotel** Chicago, Illinois

The ILLINOIS SOCIETY OF ANESTHESIOLO-GISTS announces the Twenty-Fifth Annual MID-WEST ANESTHESIA CONFERENCE. The conference is to be held on Thursday, May 12th 1988 thru Saturday, May 14th 1988 at the Hyatt Regency Hotel in Chicago, Illinois.

The three day program will present current topics in Anesthesiology in the form of mini-courses general sessions and panel discussions by renowned experts Social activities have been planned to include a tour of the new, major Anesthesiology exhibit "THE CON-QUEST OF PAIN" in the Museum of Science and Industry in Chicago.

For further information write to:

MIDWEST ANESTHESIA CONFERENCE G P Goldstein Conference Manager P.O. Box 810 Algonquin, Illinois 60102



Second International

LASER SURGERY CONGRESS

June 22-26, 1988 Opryland Hotel, Nashville, Tennessee

SPECIAL REDUCED TUITION FOR ANESTHESIOLOGISTS \$100 SATURDAY ONLY

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Meeting Location: The Congress will be held at the beautiful Opryland Hotel in Nashville, Tennessee. Right next door is Opryland, U.S.A. with live music, numerous rides, restaurants, games, shops and craftsmen. There is also the Grand Ole Opry, where top stars perform country music.

Social Activities: A cocktail hour has been planned the first night highlighting the exhibits. Also, participants of the Congress will float down the Cumberland for a dinner cruise on the General Jackson Show Boat.

Sponsored by: Department of Otolaryngology-Head and Neck Surgery and the Division of Continuing Medical Education. Congress Directors: Robert H. Ossoff, D.M.D., M.D., James A. Duncavage, M.D.

Tuition: \$425 after March 1, 1988

\$375 before March 1, 1988

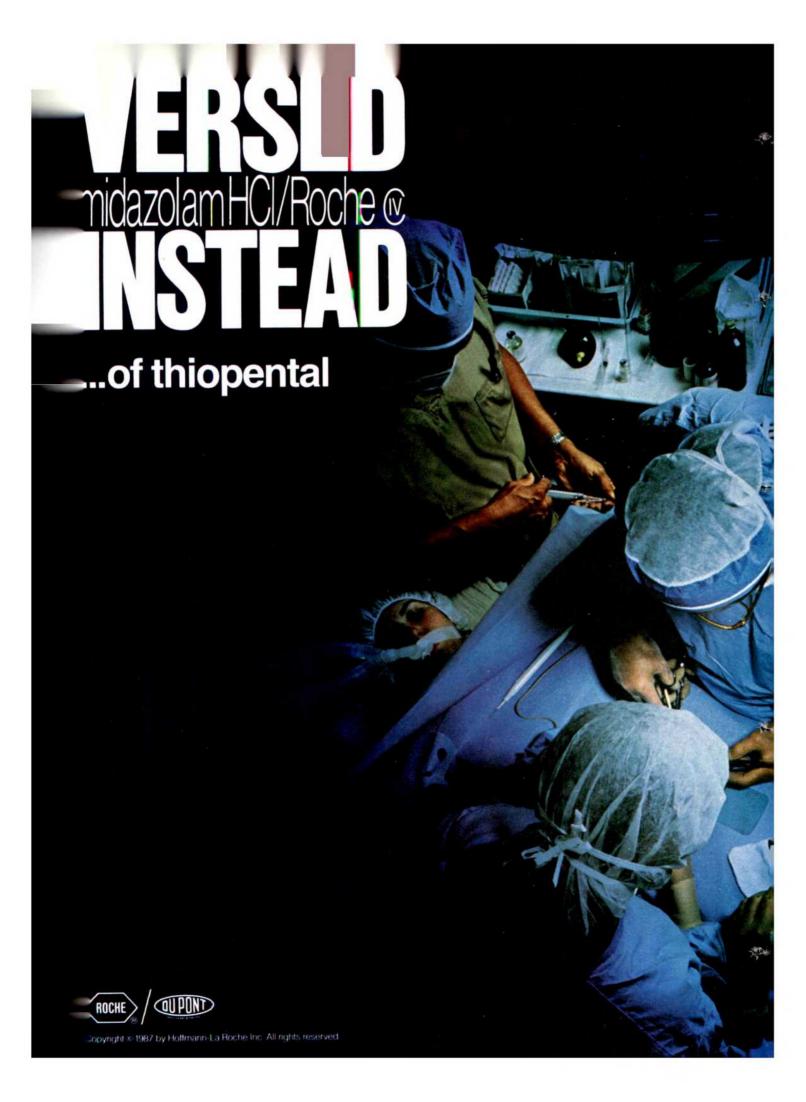
\$200 residents

\$100 Anesthesiologists/Saturday only

Additional Information: Vanderbilt Division of CME, Laser Congress Coordinator, CCC-5326 MCN, Nashville, TN 37232. (615)-322-4030.

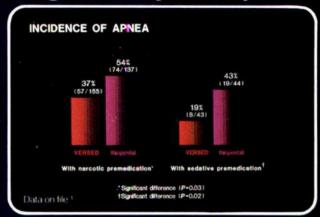


University Medical Center



Key advantages in induction

Significantly less apnea



Better hemodynamic stability

While differences were not statistically significant, VERSED I.V. produced less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance...and a less pronounced increase in mean right atrial pressure²

Pronounced anterograde amnesia

Significantly more VERSED-treated patients (24/24) had complete or partial anterograde amnesia than did thiopental-treated patients (13/26)¹

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and familiar with all dosing and administration guidelines. Reduce dosage in elderly and debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve.

INJECTABLE

INJECTABLE

Midazolam HCI

Roche (V)

A significant advance in anesthetic induction

Please see references and summary of product information on the following page:

References: 1. Data on file (Doc. #069-005, 007), Roche Laboratories. 2. VERSED* (brand of midazolam HCl/Roche) ⊚, Scientific Summary, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, NJ, 1986.

VERSED® (brand of midazolam HCI/Roche) (N INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concentration arcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower inject on. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma, may be used in open angle glaucoma only if patients are receiving appropriate therapy WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of undervenilla-tion, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle-until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation uncer light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingest on of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.

VERSED® (brand of midazolam HCI/Roche)

3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine. No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results

Carcinogenesis, mutagenesis, impairment of fertility. Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate Following IM injection: headache (1.3%), local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vorniting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%), local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory: Laryngo-spasm, bronchospasm, dyspinea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. Miscellaor reging or burning, warming recordness at injection site, fast, purities, inscena-neous: Yawning, lethargy, chilis, weakness, toothache, faint feeling, hematoma. Drug Abuse and Dependence. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam. **OVERDOSAGE:** Manifestations would resemble those observed with other benzo-

OVERDOSAGE: Manifestations would resemble those observed with other benzo-diazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

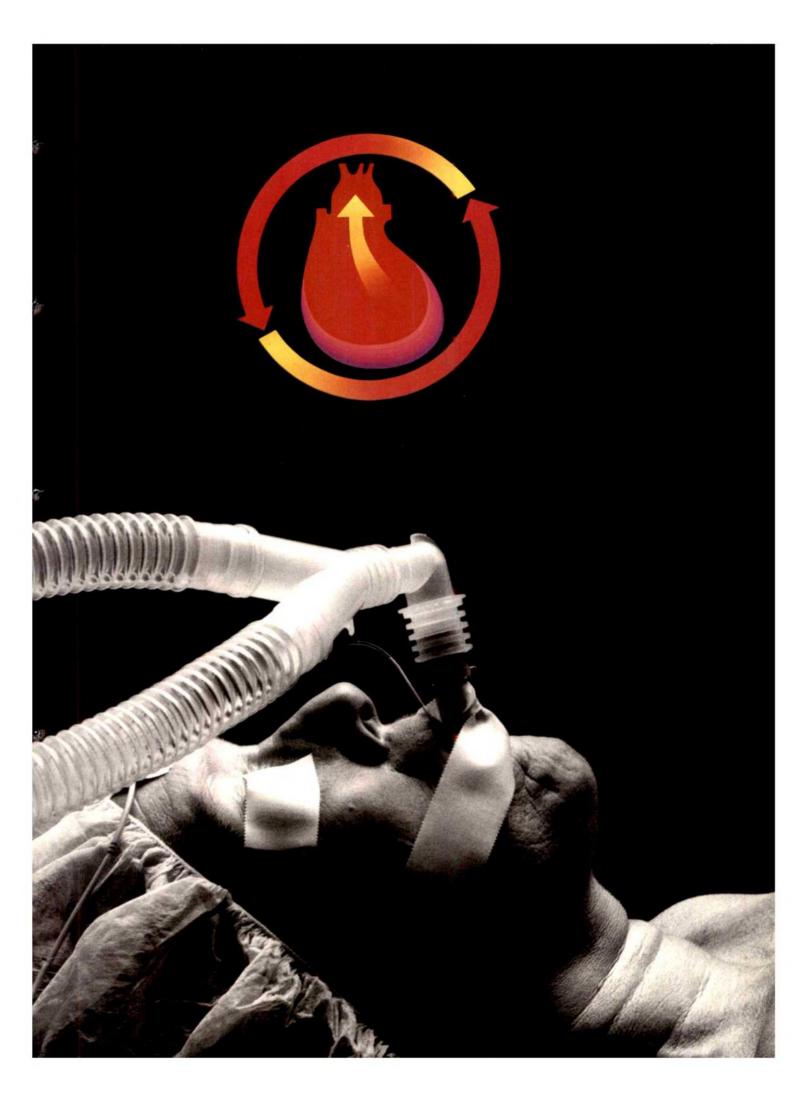
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

Roche Laboratories



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P.I. 1187



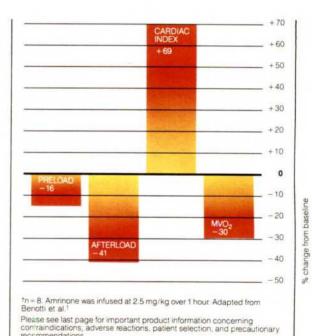
Dual action INOCOR® I.V. (AMRINONE) Inotropic plus vasodilating action in a single drug.

Two-in-one action can improve hemodynamic response after cardiac surgery.

In patients with congestive heart failure due to coronary artery disease, INOCOR LV. increases CI and decreases preload and afterload without increasing MVO₂ or significantly increasing risk of arrhythmias.

INOCOR I.V. is "...an extremely useful tool....I have been using amrinone...[for] inotropic support to wear patients from cardiopulmonary bypass and as a means of increasing [CI] in the postbypass period."*

Roberta Hines, M.D. Yale University School of Medicine Yale University Hospital



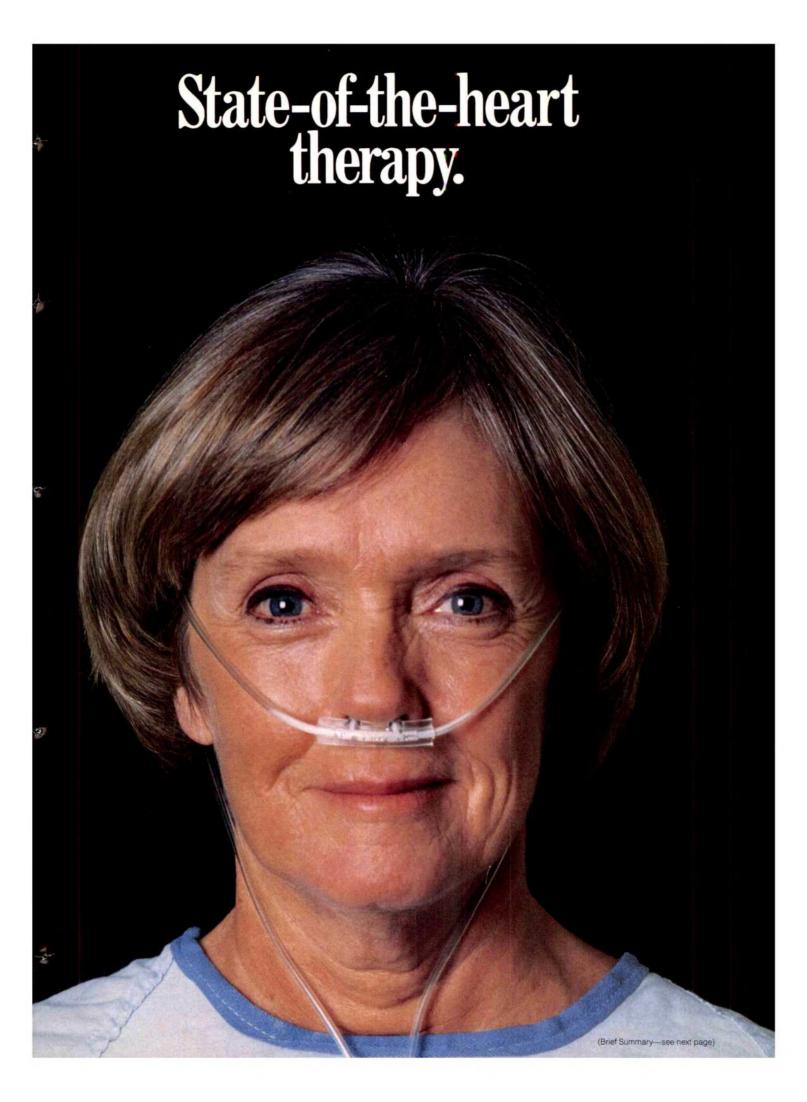
State-of-the-heart

recommendations.

*Interview on file, Winthrop Pharmaceuticals

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Dual-acting therapy, instead of catecholamines



INOCOR I.V.

Two-in-one dual inotropic and vasodilator action provides improved therapy for the cardiac surgery patient.

- Unlike catecholamines, INOCOR does not increase MVO, and can be used in ischemic patients with heart failure.
- Unlike catecholamines, INOCOR does not significantly increase risk of arrhythmias (see Precautions).
- Unlike catecholamines, INOCOR does not act on the beta receptors may be effectively used in patients on beta blockers.
- INOCOR has not been shown to interact with anesthetic agents.

Please consult full product information before prescribing. A summary follows: INOCOR factate injection, brand of aminione factate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

MOICATIONS AND USAGE (INOCOR factate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators)

closely monitored and who have not responded adequately to digitalis, diuretics, and/ov vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients.

who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites. PRECAUTIONS General: INOCOR lactate injection should not be used in

patients with severe aortic or pulmonic valuad disease in lieu of surgical relet of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis. During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients though a supersive discrepance in blood pressure.

and lear trails should be monitored and the rate of infusion slowed of stopped in patients should excessive decreases in blood pressure. Patients who have received vigorous diuretic therapy may have insuffi-cient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While arminone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs. Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE

REACTIONS). LABORATORY TESTS Fluid and electrolytes. Fluid and electrolyte changes LABURATIONY TESTS Filium and electrolytes: Fluid and electrolyte changes and renal functions should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, typokalemia should be corrected by potassium supplementation in advance of or during

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate

injection wai used concurrently with the following drugs: digitalis glycosides, lidocaine, quantidine, metoprolol, propranolol; hydralazine, prazosin, sosorbide dintrate, nitroglycerine; chlorithalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium suppliements insulin diazenam

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with

Norpace* disppyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended.

for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been

established.

USE IN PREGNANCY Pregnancy category C. In New Zealand white rabbits, aminione has been shown to produce letal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm has finding. No malformations were seen in rats receiving aminione infravenously at the maximum dose used. 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Aminione should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

to the fetus.

USE IN NUFSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in

ADVERSE REACTIONS Thrombocytopenia: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients. Gastrointestical effects. Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%). Cardiovascular effects. Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%). Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day, and 32 mg/kg/day, amrinone strowed dose-related hepatotoxicity manifested either as enzyme elevation or flepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited expenence (2.9%), following IV administration of amrinone. Hypersensitimity: There have been reports of several apparent hypersensitivity reactions in gatherts treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pencarditis, pleunits, and ascites (one case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (lone case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of

therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any

patient maintained for a prolonged period on ammone.

General: Additional adverse reactions observed in intravenous ammone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of incention (0.9%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antitode is known, but general measures for circulatory support should be taken.

measures for circulatory support should be taken MANAGEMENT OF ADVERSE REACTIONS Platelet count reductions: Asymptomatic platelet count reduction to less than '50,000/mm³) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage monthlightness.

Should a platelet count less than 150,000/mm3 occur, the following

actions may be considered:

• Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.

Decrease total daily dose.

 Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects. While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

usual benefit-fo-risk considerations.
Hepatic toxicity: In clinical experience to date with IV administration, hepatiotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amritione therapy should be promptly disconlinued.
If less than marked enzyme alterations occur without clinical symptoms, the onispects obsolute the advantage on an individual basis. The clinician may wish to continue amritione and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

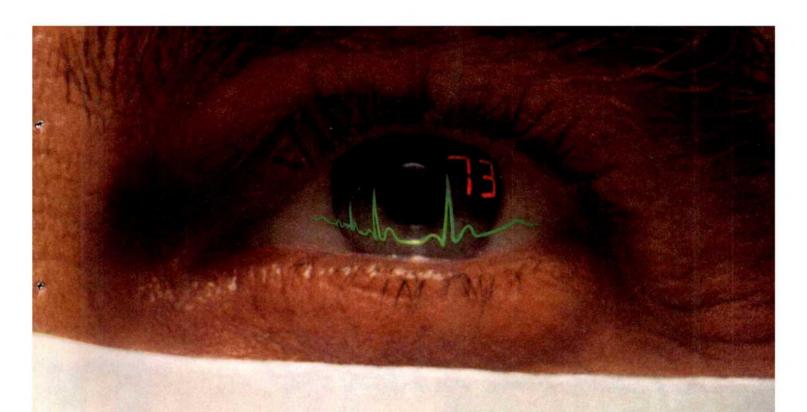
HOW SUPPLIED Amplies 0 20 mt. sterie, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.

Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. Circulation



Dual-acting therapy, instead of catecholamines



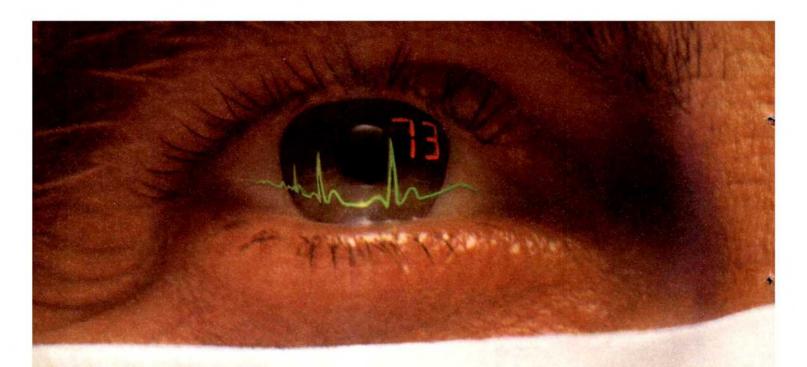


See for yourself.

The <u>only</u> surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

ideal for your patients, including those at risk.1-5

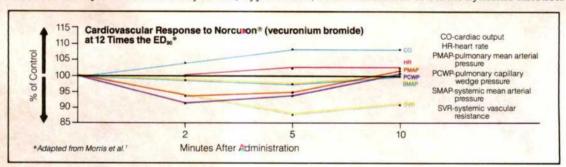




See the safety for yourself.

Free of clinically significant cardiovascular effects.*

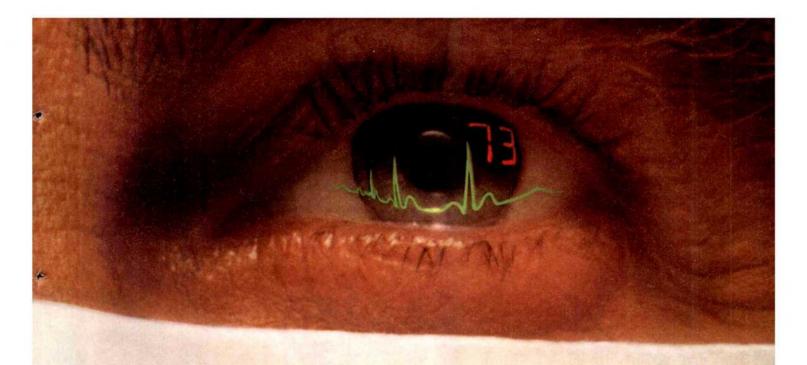
NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials. ¹⁴ In fact, even at 12 times effective doses, under halothane anesthesia, ¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{os}.5

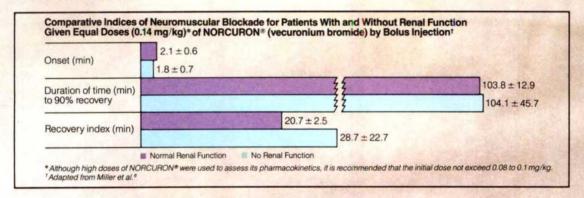
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.

Drug	Dose (mg/kg)	xED ₉₆	Histan	nine	Mean Arter Pressure	al	Heart Rate
Tubocurarine	0.5	1		410	78	9/	116
Metocurine	0.5†	2	212		79	X	119
Atracurium	0.6†	3	192	The Party of the P	80		108
Vecuronium	0.1	1.7	117			100	99
Vecuronium	0.2	3.5	87			99	102



Performance unaffected by renal function.6

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron[®] (vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1983; 88:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. Semin Anesth 1982; 1:47-56.
3. Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. Br J Anaesth 1990; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. Anesthesiology 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. Anesthesiology 1983; 58:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): Clinical Experiences with Norcuron (ORG NC 45; Vecuronium Bromide). Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron* (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

DESCRIPTION: NORCURON* (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1- $\{(2\beta \ 3\alpha, 5\alpha, 16\beta, 17\beta)$ -3. 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron* is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very limit processopic crystalline parts.

DESCRIPTION. MORCURON "exercision", and received as piperidinium, I-(28 So. 5o. 168, 178)-3. 17-bis(anxiv)cory-2-(1-piperidiniyam, I-(28 So. 5o. 168, 178)-3. 17-bis(anxiv)cory-2-(1-piperidiniyam)costosan-16-yi-1-dinivam)cory-1-dinivam (I-(28 So. 5o. 168, 178)-3. 17-bis(anxiv)cory-2-(1-piperidiniyam)costosal as a sterile nonpyropenic received-died buffered cake of very fine microscopic crystalline particles of microscopic crystalline particles of microscopic crystalline particles of the policy of the control of

Unlike other nondepolarizing skeletal muscle relaxants. Norcuron* has no clinically significant effects on hemodynamic parameters and will not counteract thase hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Petiminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

HIDICATIONS AND USAGE: Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal influbation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OF UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS, AND THE POSSIBLE COMPULCATIONS THAT MIGHT OCCUR FOLLOWING ITS USE THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have mysathenia gravis or the mysathenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron* is well-tolerated without clinically significant prolongation of neuro-muscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuro-muscular blockade may occur therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron* should be considered with slower circulation time in ca

should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron* metabolism and excretion (see Pharmacokinetics). Bata currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS. USE OF A PERPIFERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron*

agents such as vorcuron*
Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering

Norcuron* has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron* before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been syficiently shurior.

sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-fubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron*; therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patien.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with

Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

CLINICAL PHRHMACOLOGY)

Antibiotics: Parenteral/interperitoneal administration of high doses of certain antibiotics may intensity or produce neuronascular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron* during surgery unexpected prolongation of neuromuscular block should be considered a passibility.

Other: Experience concerning injection of quintidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by actiods in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade begending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of loxemia of pregnancy, may enhance the neuromuscular blockade.

Drug /Laboratory Test Interactions: None known.

may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron*. It is also not known whether Norcuron* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity Norcuron* should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron* was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of turgs pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to protound and protonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron* as with altoration from times. These adverses reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperiod. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

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The provides reactions are managed to grant yet reported, by possible with Nationary a shall advantage adequate. Little or no increase in intensity of blockade or duration of action of Noticuton* is noted from the use of this hardward and the provides an

NO REFRIGERATION REOUIRED

5% glucose in water

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC #0052-0442-57).

STORAGE: PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

SINGLE USE VIALS.

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Course Directors: Drs. Charles J. Coté, Letty M. P. Liu, Nishan G. Goudsouzian, and John F. Ryan, Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts 02114.

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Intravenous NORMODYNE® (labetalol HCl) Injection 5 mg/mL



Lowers critically high blood pressure... promptly...smoothly... reliably

- onset of response in five to ten minutes
- can be carefully controlled little risk of "overshoot"

The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as indicator of effectiveness in addition to the response of the diastolic pressure.

For Brief Summary, please see next page.

- cardiac output maintained helps assure vital organ perfusion
- helps prevent reflex tachycardia
- no intra-arterial monitoring required
- no toxic metabolite avoids cyanide toxicity
- easy to administer

Because symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within three hours of intravenous administration of labetalol, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

PRODUCT INFORMATION

NORMODYNE® brand of labetalol hydrochloride Injection

BRIEF SUMMARY

INDICATIONS AND USAGE NORMODYNE (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS
NORMODYNE (labetalol HCJ) Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia. (See WARNINGS.)

WARNINGS

Candae Failne Sympathetic stimulation is a vital component supporting circulatory function in congestive beart failure.
Gradue Failne Sympathetic stimulation is a vital component supporting circulatory function in congestive beart failure.
Beta blockade carnes a potential hazard of further depressing revocardial contractility and precipitating more severe failure.
Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalof HCL can be used with
caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in
patients receiving labetalof HCL. Labetalof HCL does not abolish the inortopic action of digitals on heart muscle.
In Patients Without a History of Cardiac Failure in patients with latent cardiac insufficiency, continued depression orithe
myocardium with beta-blocking ogents over a period of time can in some cases lead to cardiac failure. At the first sign or
symptom of impending cardiac failure, patients should be faily, digitalized and/or be given a disturct, and the response
observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. NORMODYNE (taberaloli ICC)
herpay should be withdrawn (gradually it possible).

Inchemic Hart Disease Angian pectors his not been reported upon labetalol HCl discontinuation. However, following
alexpit cessition of therapy with some beta-blocking agents in patients with contrary affects of the patients of
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patients and in some cases, myocardial infarction have been reported. Therefore, such patients should be
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Nonallerge, Branchospaum (e.g., chronic bronchitis and enaphysema) Since NORMODYNE (labetalol HCl) Injection at the usual intravenous therapeutic does has not been studied in patients with nonallergic bronchospasitic disease, it should not be used in such patients.

Phenoformoxytimal intravenous labetalol HCl has been shown to be effective in lowering the helood pressure and relieving symptoms in patients with pheochromocytoma. Buther than usual does may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Dathers Mellins and Hypoglycoma.

Dathers Mellins and Hypoglycoma. Beta-admensic blockade may prevent the appearance of premonitors signs and symptoms (e.g., tardywardia) of acute hypoglycoma. This is especially important with labile dabetics. Beta-blockade also reduces the release of insulin in response to hypoglycoma; it may director be necessary to adjust the does of anti-diabetic data of the patients of the patients

PRECAUTIONS
General Impaired Hepaire Function may diminish metabolism of NORMODYNE (labetalol HCI) Injection.
Hyptogramon Symptomatic postural hypotension (incidence 58%) in likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving NORMODYNE (labetalol HCI) Injection. Therefore, the patient's ability to tolerate an upright position within 3 hours of receiving NORMODYNE (labetalol HCI) Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.
Januakee of Hepair Dysfunction On rate occasions, oral labetalol HCI has been associated with jaunakee (both heprite and cholestatic). It is therefore recommended that treatment with labetalol HCI be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure af all possible adverse or intended effects. During and immediately following (for up to 3 hours) NORMODYNE Injection, the patient should remain suprise. Subsequently, the print architactors, and the properties of the patient is partially to become a subsequently of the patient is started on NORMODYNE Tablets, following adequate control of blood pressure with NORMODYNE Injection, appropriate directions for titration of dosage should be provided. (See DOSAGE AND ADMINISTRATION.)

As with all mags with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warramed. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physicians advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transients scalp trigling may occur, usually when treatment with NORMODYNE Tablets is initiated (see ADV-ERSE REACTIONS).

Laboratory Tests
Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCI. In patients with communitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Illnesses, such as impaired renal function, appropriate tests should be done to mornior these containing.

Drug Interactions

Since NORMODYNE (labetalol HCI) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect antifriest recomptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCI orally in combination with tricycle antidepressants experienced remor as compared to 0.3% reported to occur with labetalol HCI orally. The contribution of each of the treatments in this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drug possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with fronchospasm; therefore, doses greater than the normal anti-astimatic dose of beta-agonist bronchodilator drugs may be required.

Cinetidine has been shown to increase the bioavailability of labetalol HCI administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCI, special cause is a substitute of the patient of the patie

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheechromocytoma and being reated with labetalol HCI, specific radorenymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of
carcinogenesis. Studies with labetalol HCL using dominant lethal assays in rats and mice, and exposing microorganism
according to modified Aines tens, showed no evidence of mutagenesis.

Pregnancy Category C
Testogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations are observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adaquate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential beautiful justifies the potential risk to the fetus.

Nonteratogenic Effects
Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely
affected by the drug. Oral administration of labetalol to rais during late gestation through wearing at doses of 2 to attimes
the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Laberalol HCl given to programt women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers
Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE (labetalol HCI) Injection is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

NORMODYNE labetalol HCl) Injection is usually well tolerated. Most adverse effects have been mild and transient and in controlled traits surviving 92 patients did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is tikely to occur if patients are tilled or allowed to assume the upright position within 3 hours of receiving NORMODYNE [labetalol HCl] Injection. Moderate hypotension occurred in 1 of 100 patients while suprise. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with NORMODYNE Injection with the incidence per 100 patients as noted: Cardiovacciar System Venticular arrhythmia in 1.

Central and Pempheral Nervous Systems Dizziness in 9; tingling of the scalp/skin 7; hypoesthesia (numbness), and vertigo leach.

Central and Perpheral Nersons Systems Litzmess in 7, thinguing on six standard and caste distortion, 1 each.
Gistrometernul System Nausea in 13; vomitting 4; dispepsia and taste distortion, 1 each.
Metadock Doorders Transent increases in blood urea nitrogen and seniam creatinine levels occurred in 8 of 100 patients;
these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.
Psychiams Disorders Soundeneelyawaring in 3.
Respiratory System Wheering in 1.
Sinn Purities in 1.
The incidence of adverse reactions depends upon the dose of labetalol HCL. The largest experience is with oral labetalol
HCL (see NORMODYNE Table Product Information for details). Certain of the side effects increased with increasing oral
dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are
clearly or possibly dose related.

rateging on Pressions according									
Labetalol HCl Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1		4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	I	0	2	2	4
Paresthesias	2	0	2	2	1	1	2:	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	ė.	2	1	2	3	0	4	3	5
Impotence	T	1	1	- 1	2	4	3.	4	3
Edema	1	0	Î	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCI uring investigational use and extensive foreign marketing experience. Clinical laboratory tests: Among gatients dosed with NORMODYNE (labetalol HCI) Tablets, there have been reversible streams of serim intransminuses in 4% of patients tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCI) Injection causes excessive hypotension that is posture sensitive, and sometimes, excessive bradycarda. Panenus should be placed signine and their legs raised if necessary to improve the blood supply to the brann. If overdosage with labetalol HCI follows onli ingestion, gastric lavage or pharmacologically induced emess (using syrup of peeca) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed in necessary: Excessive bradycandar—administer admipute or epithemic. Cardiac juliar—administer adjustals glycoside and a dustric. Dopamine or dobustamine may also be useful. Hypotension—administer exappressors, e.g., norepirephrine. There is phirmacological evidence that norepirephrine may be the drug of choice. Bronchopam—administer epinephrine and/or an aerosolized betay-agonist. Scrares—administer diacepam. In severe beta-blocker overdose resulting in hypotension and/or bandycarda, glucagon has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor pentroneal dialysis removes a significant amount of labetalol HCI from the general circulation (et 18).

e patient improves). Idialysis nor peritorical dialysis removes a significant amount of labetalol HCl from the general circulation

5.1%). The oral LD₅₀ value of labetalol HCI in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The travenous LD₅₀ in their species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

NORMODYNE (laberalol HCI) Injection is intended for intravenous use in hospitalized patients. DOSAGE MUST BE

RDIVIDUALIZED depending upon the seventry of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of intravenous drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to rolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of NORMODYNE (labetalol HCI) Injection should be given in a dose of 20 mg labetalol HCI (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous injection over a two-minute period. Immediately before the injection and at five and ten minutes after injection, spitne blood pressure should be measured to evaluate response. Additional injections of 40 mg or 80 mg can be given at ten minute intervals until a desired supine blood pressure is sold the investment of 30 mg labetalol HCI has been injected. The maximum effect usually occurs within 3 minutes of each injection.

Sinu Continuous influsion. NORMODYNE (labetalol HCI) Injection is prepared for intravenous continuous infusion by diluting the contents with commonly used intravenous fluids (see below). Examples of methods of preparing the unknown

Slow Continuous Infision. NORMODYNE (labetalol HCD) Injection is prepared for intravenous continuous infusion by duluting the contents with commonly used intravenous fluids (see below). Examples of methods of preparing the infusion solution are:

The contents of either two 20 ml vials (40 ml), or one 40 ml vial, are added to 160 ml of a commonly used intravenous fluid such that the resultant 200 ml of solution contains 200 mg of abetalol HCl. 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, the contents of either two 20 ml vials (40 ml), or one 40 ml vial, of NORMODYNE (labetalol HCl) Injection are added to 250 ml of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl. approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To bacilitate a desired rate of infusions, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burrett or mechanically driven infusion pump.

Since the half life of labetalod a 5 to 8 hours, seady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and onal labetalol HCl statered (see helow). The effective intravenous done is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients of the infusion or intravenous injections. Rapid or excesser falls in effective should be a more particular in some patients.

Blood Pressure Monatomy The blood pressure should be continued in spirit particular intravenous treatment should be analysed. In patient patient of the patients of the patients of the response of the distribution of the response of the distribution and pressure response has begin to rise. The recommended initial dose is 20

inpatient Litrat	ion instructions	
Regimen	Daily Dose*	
200 mg bid	400 mg	
400 mg bid	800 mg	
800 mg bid	1600 mg	
1200 marked	7400 me	

'If needed, the total daily dose may be given in three divided doses

While in the hospital, the dosage of NORMODYNE Tablets may be increased at one day intervals to achieve the desired god pressure reduction.

neous pressure resuction.

For subsequent outpatient titration of maintenance dosing see NORMODYNE Tablets Product Information DOSAGE AND ADMINISTRATION for additional recommendations.

AND ADMINISTRATION for additional recommendations.

Compatibility with commonly used intravenous fluids parenteed in the products should be inspected visually for particulate matter and discoloration prior to administration, whenever solutions and container permit.

NORMODYNE (laberaled HCD) Injection was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg to 3.75 mg labetalol HCL per ml of the mixture, NORMODYNE Injection was found to be compatible with and stable for 24 hours refingerated or at room temperature) in mixtures with the following solutions: Ringen Injection, USP

5% Dextrose and Ringers Injection, USP

5% Dextrose and Ringers Injection, USP

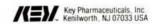
5% Dextrose and 0.24% Sodium Chloride Injection, USP

5% Dextrose and 0.24% Sodium Chloride Injection, USP

5% Dextrose and 0.35% Sodium Chloride Injection, USP

NORMODYNE (labetalol HCL) Injection was NOT compatible with 5% Sodium Bicarbonate Injection, USP.

HOW SUPPLIED
NORMODYNE (laberalol HCI) Injection, 5 mg/ml, is supplied in 20 ml (100 mg) (NDC-0085-0362-07) and 40 ml (200 mg) (NDC-0085-0362-06) multi-dose vials, boxes of L
Store between 2° and 30°C (36° and 86°F). Do not freeze.



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Antihypertensive Mechanism of Ketanserin in Postoperative Hypertension After Cardiopulmonary Bypass

Christian Anger, MD, John A. Carter, MB, BS, FFARCS, and Cedric Prys-Roberts, DM, PhD, FFARCS, FFARACS

ANGER C, CARTER JA, PRYS-ROBERTS C. Antihypertensive mechanism of ketanserin in postoperative hypertension after cardiopulmonary bypass. Anesth Analg 1987;67:99–106.

The effect of ketanserin (0.15 mg/kg followed by an infusion at 6 mg/hr) was studied in 13 patients who developed hypertension (blood pressure > 150/90 mm Hg) after cardiopulmonary bypass (CPB) for coronary artery bypass grafting. Eleven patients responded to ketanserin with a decrease of arterial pressure from $159 \pm 15/83 \pm 10$ mm Hg to $131 \pm 9/70 \pm 12$ mm Hg (P < 0.01), which was sustained during the subsequent infusion of ketanserin. Mean plasma ketanserin concentrations were maintained at $187 \mu g/L$ (range 118-525). No significant changes in plasma levels of 5-hydroxyindoles or in platelet 5-hydroxytryptamine content were observed during or after

CPB, or after administration of ketanserin. Plasma epinephrine (398 \pm 124 pg/ml) and norepinephrine (1161 \pm 673 pg/ml) concentrations were markedly increased during the hypertensive period after CPB. Plasma epinephrine concentrations decreased (P < 0.01) during ketanserin infusion to 213 \pm 101 pg/ml, whereas plasma norepinephrine concentrations did not change. The pressor response to three graded doses of phenylephrine was decreased during CPB (P < 0.01), and a further decrease (P < 0.05) occurred during infusion of ketanserin. The hypotensive effect of ketanserin after CPB may be attributable to alpha_1-adrenoceptor blockade rather than to its antiserotoninergic effect. Serotonin does not appear to be involved in the short-term disturbances of arterial pressure during or after CPB.

Key Words: SEROTONIN—ketanserin. PHARMACOLOGY—ketanserin. ANESTHESIA, CARDIOVASCULAR—ketanserin.

It has been known for more than a century that when blood coagulates its serum exhibits vasoconstrictive properties. In 1948, Maurice Rapport (1) identified the vasoconstrictor substance as being 5-hydroxytryptamine and named it, accordingly, serotonin.

Serotonin has been implicated as an etiologic factor in the pathophysiology of hypertension (2), and specific serotonin antagonists such as ketanserin have been investigated as antihypertensive drugs (3). Hypertension is common after cardiopulmonary bypass for myocardial revascularization (4–6), and a number of factors have been implicated (7–12). Van der Starre et al. (13) found that ketanserin lowered

arterial pressure in patients after coronary bypass surgery. Although ketanserin has been shown to exert both serotonin and alpha₁-adrenoceptor antagonism (14), the title of the paper by Van der Starre et al. (13) implied that the hypotensive effect of the drug was related to antiserotoninergic properties. In a previous publication (15), we showed that there were no significant changes of plasma 5-hydroxyindoles or platelet 5-hydroxytryptamine during or after coronary artery surgery. We have therefore investigated the antihypertensive mechanism of ketanserin in patients after coronary artery bypass surgery.

Methods

Thirteen patients undergoing cardiopulmonary bypass (CPB) for coronary artery bypass grafting (CABG) were investigated. The patients' ages ranged from 46 to 75 years (mean 56), and their weights ranged from 60.2 to 88.5 kg (mean 73.6). The study was approved by the Ethics Committee of the Bristol

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and Weston Health District, and by the Committee on the Safety of Medicines (United Kingdom). All patients consented to the study after a full explanation of the procedures.

All patients continued to receive their normal medication up to and including the morning of surgery. None was receiving any medication that would have interfered with serotonin uptake or metabolism (e.g., MAO-inhibitors, tricyclic antidepressants, reserpine, benzoquinolizines, biguanidines, ergot alkaloids, methysergide, or 5-HT antagonists). Premedication consisted of papaveretum 15-20 mg and hyoscine 0.3-0.4 mg IM. Anesthesia was induced with phenoperidine 2-4 mg or fentanyl 5-10 μg/kg and thiopental according to clinical requirements. After muscle relaxation with pancuronium bromide (0.15 mg/kg), patients were intubated and mechanically ventilated initially with 50% nitrous oxide in oxygen. Inspiratory oxygen concentration was further adjusted according to clinical requirements and repeated blood gas analysis. Anesthesia was maintained by incremental doses of phenoperidine (2-4 mg/hr) or an infusion of fentanyl at 15 μ g · kg⁻¹ · hr⁻¹.

Monitoring included ECG, central venous pressure (CVP), arterial blood pressure (BP) by cannulation of the radial artery and, after CPB, left atrial pressure (LAP). After heparinization, CPB was started using a nonpulsatile roller pump and a disposable bubble or membrane oxygenator. The calculated flow rate was scaled to 2.4 L · m⁻² and the extracorporeal system was primed with 2-2.5 L of Hartmann's solution. Infusion of cardioplegic solution in the aortic root immediately after aortic crossclamping and intermittently during CPB was carried out for myocardial protection. Patients' temperatures were cooled to 25-27°C during extracorporeal circulation and rewarmed to 37°C at its end. Protamine sulfate was used for neutralization of heparin at the termination of CPB.

Postoperatively, all patients were transferred to the cardiac care unit, kept intubated, and ventilated with an appropriate inspiratory oxygen concentration. During early recovery all patients had blood pressure > 150/90 mm Hg and were given a single injection of 0.15 mg/kg ketanserin sustained by an infusion of 6 mg/hr over 30 minutes.

The pressor responses to single doses of phenylephrine (15, 30, and 45 μ g) were studied before CPB, after CPB, and during infusion of ketanserin provided there was:

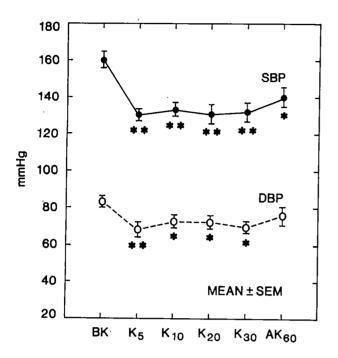
 good left ventricular function not requiring support by positive inotropic drugs and/or vascular resistance reduction by sodium nitroprusside;

- 2. a normal left atrial pressure;
- 3. no cardiac arrhythmia;
- no evidence of myocardial ischemia in the ECG (lead CM 5);
- 5. arterial pressure in an acceptable range (systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg).

The three doses of phenylephrine, an alpha₁-adrenoceptor agonist, were selected after experience of their use in other clinical circumstances. The increase of systolic arterial pressure induced by the maximum dose of phenylephrine (45 μ g) was less than that normally observed in response to surgical stimuli such as sternotomy, and had not previously been shown to cause myocardial ischemia.

One or 2 days before surgery a baseline venous blood sample (PRO) was taken during the early morning from a forearm vein. During and after surgery, blood samples were collected from a central venous catheter at the following times: before cardiopulmonary bypass (BB), after 5 minutes on bypass (B1), after 60 minutes on bypass (B2), after bypass, 10 minutes after the administration of protamine sulfate (PB), postoperatively, immediately after arrival in the cardiac unit (PO), before injection of ketanserin (BK), and during infusion of ketanserin for 5, 10, 20, and 30 minutes (K5, K10, K20, and K30). Blood samples were stored on ice and centrifuged at 4°C within 30 minutes. The platelet-rich plasma supernatant was centrifuged at high speed to separate platelets from plasma, and both pellet and plasma sample were immediately frozen in liquid nitrogen. An aliquot of each was analyzed for platelet count.

Serotonin was assayed by a modification of the spectrofluorimetric assay of Drummond and Gordon. We have described sample preparation and modification of the assay in detail elsewhere (15). Because the spectrofluorimetric assay does not allow discrimination between the main circulating precursor 5hydroxytryptophan and 5-hydroxytryptamine (5-HT), nor the main metabolite 5-hydroxyindole acetic acid, plasma serotonin concentrations are therefore expressed as nanograms of 5-hydroxyindoles (5-HI) per milliliter of plasma. Platelets contain only 5-HT, and their contents are expressed as nanograms of 5-HT per 2×10^8 platelets. Plasma levels of epinephrine and norepinephrine were assayed by normalphase high pressure liquid chromatography (HPLC) with electrochemical (16) detection. The lowest limits of detection were 21 pg/ml (coefficient of variation 7.6% at 200 pg/ml for norepinephrine and 42 pg/ml (coefficient of variation 6.5%) for epinephrine. Plasma ketanserin concentrations (BK) to K30) were assayed by HPLC with fluorimetric detection (17).



<u>Figure 1</u>. Changes in systolic and diastolic blood pressure after a single IV injection of ketanserin sustained by an infusion of ketanserin in patients with postoperative hypertension (mean \pm sem). *P < 0.05, **P < 0.01 as compared with before injection of ketanserin. For abbreviations of episodes see text.

Statistical analysis was performed using the Friedman test and the test of Wilcoxon and Wilcox for paired samples; P < 0.05 was considered statistically significant. All results are expressed as mean \pm sp.

Results

Anesthetic time averaged 397 minutes (range 280 to 460). Total perfusion time ranged from 114 to 187

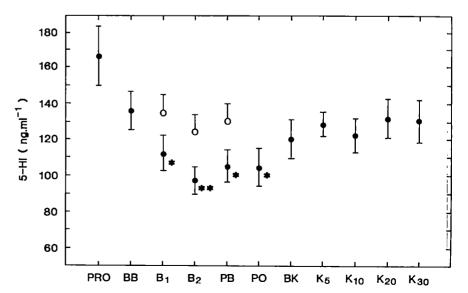
minutes with an average of 150 minutes. The minimum number of coronary artery bypass grafts performed as two (one sequential); the maximum was five grafts. All patients were receiving either beta-adrenoceptor antagonists (propranolol, three patients; atenolol, four patients) and/or calcium-channel blockers (nifedipine, seven patients; verapamil, four patients).

Every patient had an increase of systolic blood pressure to 150 mm Hg or higher during early recovery. The IV injection of 0.15 mg/kg ketanserin sustained by an infusion of 6 mg/hr over 30 minutes resulted in a significant decrease of systolic and diastolic arterial pressures in 11 patients from 159 \pm 15/83 \pm 10 mm Hg to 131 \pm 9/70 \pm 12 mm Hg, but failed to do so in two patients, one of whom had a kr.own history of hypertension since 1980. Blood pressure decreased rapidly after the initial ketanserin dose and was maintained in a clinically acceptable range during the 30-minute infusion period, with a slight increase thereafter (Fig. 1).

Heart rate and left atrial pressure decreased slightly during infusion of ketanserin (87 ± 10 to 81 ± 12 beats/min and 11.6 ± 5.0 to 9.3 ± 4.8 mm Hg, respectively), with the latter reaching statistical significance after 10 minutes of infusion. The baseline plasma 5-HI concentrations ranged between 70 and 250 ng/ml (mean 166). The decrease in 5-HI levels before bypass below baseline levels was due to volume replacement during anesthesia. There was a significant decrease of plasma 5-HI concentrations during bypass that, when corrected for the pump priming volume, was no longer significantly different from the levels seen before bypass (Fig. 2).

At the same time there was an increase in platelet

Figure 2. Plasma 5-HI concentrations (mean \pm sem) before, during, and after CPB. **P < 0.05, **P < 0.01 as compared with values before CPB. (\bullet) Uncorrected data; (O) corrected for hemodilution. For abbreviations of episodes see text.



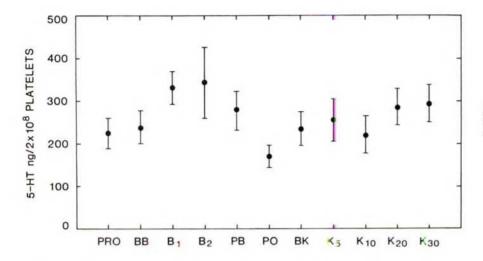


Figure 3. Platelet 5-HT content (mean ± sem) before, during, and after CPB. For abbreviations of episodes see text.

5-HT content from 241 ± 103 ng per 2×10^8 platelets before bypass to 345 ± 227 ng per 2×10^8 platelets during CPB (not significant). After the administration of protamine sulfate, platelet 5-HT content returned to levels not significantly different from those seen before bypass (Fig. 3). Plasma 5-HI concentration was also similar to prebypass levels during early recovery and no significant change could be observed, nor was there a significant correlation between plasma 5-HI concentration and either systolic or diastolic blood pressure. Plasma 5-HI levels were not affected by infusion of ketanserin (Fig. 2).

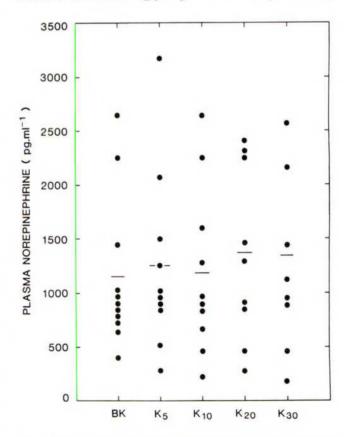
By contrast, plasma norepinephrine and epinephrine concentrations were very high postoperatively (1161 \pm 673 pg/ml and 398 \pm 124 pg/ml), though with a wide distribution of individual values (Fig. 4). No significant changes in norepinephrine levels occurred during the 30-minute infusion of ketanserin, whereas plasma epinephrine concentrations significantly decreased to (213 \pm 107 pg/ml) during infusion of ketanserin (Fig. 5).

According to our entry criteria, a phenylephrine dose-response study could only be performed in seven patients postoperatively; high arterial pressure, cardiac arrhythmias, or impaired ventricular performance occurred in the other six patients. The increase of systolic BP to the three doses of phenylephrine was significantly less after bypass at the 30-and 40-µg doses (Fig. 6). During infusion of ketanserin there was a further decrease in the systolic BP response to phenylephrine that was significant after the 30-µg dose, but not after the 15- and 45-µg doses.

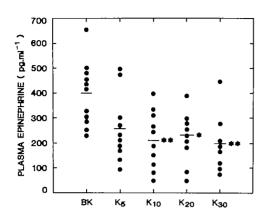
Mean plasma ketanserin concentrations ranged from 93 to 334 μ g/L (mean 206) after the initial injection and 5-minute infusion of ketanserin. After 30 minutes of infusion of ketanserin, plasma concentrations ranged from 118 to 535 μ g/L (mean 187).

Discussion

Postoperative hypertension after myocardial revascularization is a frequently encountered problem (5–7) and is, in general, due to a marked increase in systemic vascular resistance (4). Plasma levels of endogenous vasopressors such as norepinephrine, vasopressin (ADH), and angiotensin II have been found to be exceedingly high after cardiopulmonary



<u>Figure 4</u>. Norepinephrine concentrations during early recovery, before, and during infusion of ketanserin. Mean values indicated by horizontal lines. For abbreviations of episodes see text.

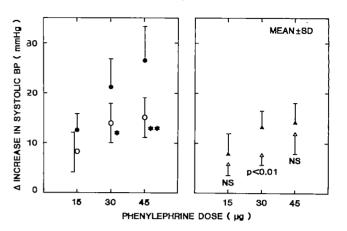


<u>Figure 5</u>. Epinephrine concentrations during early recovery, before, and during infusion of ketanserin. Mean values indicated by horizontal lines. $^*P < 0.05$, $^{**}P < 0.01$ as compared with before injection of ketanserin. Abbreviations as in Fig. 4.

bypass and during early recovery (8–12). Our findings of very high plasma norepinephrine and epinephrine concentrations during early recovery confirm this phenomenon.

Like Van der Starre et al. (13) and Miranda et al. (14), we found that ketanserin significantly decreased systolic and diastolic blood pressure in patients recovery from myocardial revascularization. Arterial pressure was maintained in a clinically acceptable range by the sustained infusion of ketanserin. Two of our 13 patients did not respond to ketanserin and an infusion of sodium nitroprusside had to be started. Griffiths and Whitwam (18) observed a lower mean arterial systolic pressure 15 minutes after starting an infusion of ketanserin (60 μ g · kg⁻¹ · hr⁻¹) before cardiopulmonary bypass and a lower mean systolic and diastolic pressure immediately after bypass, but not during the following hours or during the time of bypass. Many studies in humans, patients and volunteers have shown a blood pressure lowering effect of ketanserin (2,3,18-23). However, the implication that ketanserin is a valuable tool for the investigation of 5-hydroxytryptamine-induced pathology is not yet supported by reliable evidence.

In vitro studies have shown that ketanserin exerts alpha-adrenoceptor antagonist activity in a concentration five times that required to block 5-HT $_2$ receptors (24,25). Wenting et al. (2) were unable to observe a shift of the phenylephrine dose-response curve up to doses of 100 μ g, measured as an increase in mean arterial pressure, after an intravenous injection of 10 mg ketanserin, sustained by an infusion of 2 mg/hr. However, they found the antihypertensive effect of ketanserin blunted by pretreatment with prazosin, an alpha₁-adrenoceptor antagonist, in patients with essential hypertension (19). Others have shown a significant decrease of the pressor response to methoxa-



<u>Figure 6</u>. Pressor responses to phenylephrine before and after cardiopulmonary bypass (left panel, n=7), and before and during infusion of ketanserin (right panel, n=7) (mean \pm sp; *P<0.05, **F<0.01). (\blacksquare) pre-bypass; (\square) post-bypass; (\square) pre-ketanserin; (\square) post-ketanserin.

mene both in patients and healthy volunteers given 40 mg ketanserin orally twice daily (20) or 0.15 mg/kg IV (3.20). Other data suggest that alpha₁-adrenoceptor blockade occurs in humans with the doses of ketanserin used clinically (26).

Griffiths and Whitwam performed repeated norepinephrine dose-responses in patients during cardiopulmonary bypass and found a marked reduction in the effect of norepinephrine after ketanserin, which was highly significant at all three dose levels (27). Plasma ketanserin concentrations of 90 μ g/L were shown to shift the response to methoxamine significantly to the right, indicating alpha₁-adrenoceptor blockade (20). Plasma ketanserin concentrations in our study were well above this level throughout the infusion.

In animal studies, the antihypertensive effect of ketanserin occurred in doses that block alpha₁receptors, but not at lower doses that block serotonin receptors (28-30). The antihypertensive effect of ketanserin in the rat is probably due to antagonism of vascular alpha₁-adrenoceptors (30). More specific serotonin antagonists, which do not block alphaacrenoceptors in vivo, do not lower blood pressure; and the reduction in blood pressure produced by a series of serotonin receptor antagonists correlated with their ability to block alpha₁-adrenoceptors, but not 5-HT2-receptors (31,32). Increased plasma 5-HT concentration released from damaged platelets has been suggested to be the cause (13,14). However, we have found no significant changes in either plasma levels of 5-hydroxyindoles or in platelet 5-hydroxytryptamine concentrations at any time after bypass either in this or in our previous study (15).

In the present study we found plasma 5-HI concentrations decreased significantly during the time of bypass (Fig. 2), reflecting the effect of hemodilution. because when corrected for the pump priming volume, the concentrations were not significantly different from the prebypass values. Shida et al. (33) measured plasma serotonin concentrations of the order of 240 ± 40 ngml before CPB, which decreased to 120 ± 50 ng/ml during the time of bypass and to 130 ± 40 ng/ml during surface-induced deep hypothermia. They found plasma serotonin levels decreased significantly during extracorporeal circulation, even when corrected for 25% hemodilution, and also during deep hypothermia, but found no significant difference in plasma serotonin concentrations in patients with or without postoperative low cardiac output syndrome or pulmonary hypertension.

Cashman et al. (23) measured plasma 5-HI concentrations of the order of 157 to 252 ng/ml before sternotomy and found no significant change for up to 10 minutes after sternal spread. Shuttleworth and O'Brien (34), also using a fluorimetric assay, found mean plasma 5-HI levels to increase with age from 73 ng/ml in 20- to 29-year-old patients to 126 ngml in 60- to 69-year-old subjects. We found plasma 5-HI concentrations of 166 ± 60 ng/ml preoperatively and 136 ± 40 ng/ml before CPB, which decreased to 97 ± 8 ng/ml during CPB.

We found no significant differences in plasma 5-HI and platelet-bound 5-HT between patients with or without postoperative hypertension, nor could we find a significantly correlation between plasma 5-HI concentration and either systolic or diastolic blood pressure. Up to 3 hours postoperatively we observed no significant changes in plasma 5-HI levels or platelet 5-HT content as compared with baseline; Shida et al. (33) also found no significant changes in plasma serotonin concentrations for up to 3 days postoperatively. The vasomotor response to free plasma serotonin is dependent on mediators such as prostacyclin and thromboxane A, which are synthesized in the endothelial cell. It has been suggested that the response to 5-hydroxytryptamine is the net result of a direct contractile action on smooth muscle and an inhibitory action mediated by the endothelium (35,36). The existence of a "physiologic" level of free plasma serotonin is very much in question and does not seem to underly any feedback control (37,38)

During CPB, platelet 5-HT content increased (Fig. 3), as shown in our previous study (15). The relatively large amounts of platelet-bound 5-HT detected in our assay have been discussed elsewhere. Although Parbtani et al. (39) state that when handled properly the amount of 5-HT in platelets does not change for

hours, and though Lingjaerde (40) recommends centrifuging samples at room temperature, serotonin efflux from platelets is highly temperature dependent. Our samples were centrifuged at 4°C immediately, which may in part account for the differences between our data and those reported by others. Almost all circulating 5-hydroxytryptamine is contained within platelets (36,41) and free plasma 5-hydroxytryptamine is avidly taken up by the surrounding endothelial cells and platelets. Sequestration of platelets occurs during CPB and most of them are returned into the circulation of up to 2 hours after extracorporeal circulation (42). Depending on the type of oxygenator used and the effect of the suction systems, 70-95% of platelet sequestration is reversible (33). Postoperatively, platelet 5-HT levels decreased in our patients to about prebypass levels, consistent with platelet aggregation, probably at the sites of injury.

Vascular responsiveness to alpha-adrenergic stimulation was significantly decreased after cardiopulmonary bypass as shown by the decreased pressor response to phenylephrine, in agreement with recent findings (43). We found a decreased pressor response to phenylephrine during infusion of ketanserin (Fig. 6). Griffiths and Whitwam (27) found the increase in mean arterial pressure after 100, 200, and 300 μg phenylephrine to be less after ketanserin when given during cardiopulmonary bypass, but the comparable responses were not statistically significant from their control values (27). However, the same authors showed a highly significant reduction in the effect of norepinephrine on mean arterial pressure after administration of ketanserin into the perfusion system, indicating alpha-adrenoceptor blockade (18).

A surprising finding was the decrease of plasma epinephrine levels, but not norepinephrine levels, after a 10-minute infusion of ketanserin (Fig. 5). Given that the hypotensive effect of ketanserin in these patients cannot be explained totally on the basis of either the antiserotoninergic effect or the alpha₁-adrenoceptor antagonism, we question whether the reduction in plasma epinephrine could account for the mild antihypertensive response.

We did not measure cardiac output in our patients and thus were not able to calculate systemic vascular resistance. Left atrial pressure decreased during infusion of ketanserin and heart rate also decreased during infusion of ketanserin, an observation made by many (20–22,26), though not by all investigators (3.19)

In conclusion, in the presence of arterial hypertension after CPB, the injection of 0.15 mg/kg ketanserin resulted in a significant reduction of systolic and

diastolic blood pressures, which was maintained in an acceptable range by an infusion of 6 mg/hr ketanserin. The hypotensive effect of ketanserin after intravenous injection could be accounted for by alpha₁-adrenoceptor blockade. Plasma serotonin did not appear to be involved in the short-term regulation of cardiovascular homeostasis during and after cardiopulmonary bypass, which was associated with decreased vascular responsiveness to alpha-adrenoceptor stimulation.

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Cardiac Electrophysiologic Effects of Lidocaine and Bupivacaine

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MOLLER RA, COVINO BG. Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 1988:67:107–14.

The cardiac electrophysiologic effects of bupivacaine (B) and lidocaine (L) were evaluated in an isolated rabbit Purkinje fiber-ventricular muscle model to determine the effects of a) progressively increasing and b) decreasing concentrations of B and L on transmembrane action potentials. Bupivacaine (3 and 5 µg/ml) significantly decreased diastolic resting potential, maximum rate of depolarization, and action potential amplitude. Lidocaine (10–20 µg/ml) also de-

creased maximum rate of depolarization and action potential amplitude, but the decreases were significantly different from those produced by B. High concentrations of B (30 µg/ml) and L (100 µg/ml) resulted in delayed conduction between Purkinje fibers and ventricular muscle cells and, ultimately, conduction blockade. The duration of conduction blockade was significantly longer with B than with L. The results of this study indicate that B produces electrophysiologic changes in cardiac tissue that may produce ventricular arrhythmias of a reentrant type.

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine. HEART—bupivacaine, lidocaine.

Excessive doses of all local anesthetic agents may cause myocardial depression (1). In addition, certain local anesthetic drugs such as bupivacaine have been reported to induce cardiac arrhythmias that may be responsible for the sudden cardiovascular collapse reported in some patients after the accidental intravascular injection of bupivacaine (2–5). Ventricular arrhythmias have been observed with bupivacaine but not with lidocaine in isolated cardiac preparations (6) and in a variety of intact animals (7–11).

A number of electrophysiologic studies have attempted to determine the etiology of bupivacaine-induced ventricular arrhythmias. Clarkson and Hondeghem (12,13), using an isolated guinea pig papillary muscle preparation, found that both lidocaine and bupivacaine cause rate- and dose-dependent decreases in the maximum rate of depolarization (V max). The effect of bupivacaine was more pronounced than that of lidocaine. Lynch (14) reported similar findings, although the degree of V max depression with both drugs was less than that observed by Clarkson and Hondeghem. These differ-

ences may be related to the use of different buffer solutions (15). Clarkson and Hondeghem also reported that recovery from drug-induced depression was significantly longer with bupivacaine than with lidocaine. Thus it was postulated that bupivacaine produces a "fast in–slow out" type of depression of sodium conductance, whereas lidocaine was characterized as causing a "fast in–fast out" type of depression. The slow recovery of sodium channel blockade by bupivacaine was believed to be responsible for the arrhythmogenic activity of bupivacaine.

Electrophysiologic alterations other than those involving the rate of depolarization may also lead to arrhythmias. Little information is available concerning the effect of bupivacaine on diastolic resting potential, action potential duration, membrane responsiveness, and conduction between Purkinje fibers and ventricular muscle. The present study was initiated to determine the effects of lidocaine and bupivacaine on the electrophysiologic properties of both Purkinje fibers and ventricular muscle. On the basis of these studies it appears that bupivacaine has the ability to induce a reentry type of ventricular arrhythmia and profound PF-VM conduction block.

Methods

Male New Zealand rabbits weighing 2–3.5 kg were killed by the intravenous injection of air. A thoracot-

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omy was performed and the heart was quickly removed and placed in cool Tyrode's solution aerated with 95% O₂ and 5% CO₂ to obtain a pH of 7.35 at 37°C. The Tyrode's solution contained (in mM/L) NaCl, 137; KCl, 4.5; CaCl₂, 1.8; MgCl₂, 0.9; NaHCO₃, 25; NaH₂PO₄, 1.2; glucose, 11. The right ventricular septal wall, including the right bundle branch and papillary muscles, was dissected out, placed in a Lucite chamber, and superfused at a rate of 10 ml/min with Tyrode's solution maintained at a temperature of 37°C.

Recording glass microelectrodes filled with 3 M KCl with tip diameters of $<1 \mu m$ were inserted into Purkinje fiber cells and ventricular muscle cells one to two layers deep to minimize diffusional problems using methods previously reported (16). The action potentials were passed through a wideband electrometer and the Purkinje fiber and ventricular muscle potentials simultaneously displayed on an oscilloscope. The preparation was paced at a rate of 2.5 Hz with bipolar Teflon-coated silver wires delivering rectangular pulses of 1 msec duration and an amplitude two times that required to elicit a response during diastole, i.e., twice threshold. The following measurements were made: maximum diastolic potential (MDP) in mV, action potential amplitude (AP) in mV, maximum rate of depolarization (V max) cbtained from an electronically differentiated first derivative in V/sec, and action potential duration (APD) at 50 and 75% repolarization in msec.

Effective refractory period (ERP) was determined by applying a rectangular impulse of 2 msec duration and three times threshold directly to the Purkinje fiber or ventricular muscle at various intervals following the depolarization phase. The shortest coupling interval that elicited a premature response was defined as the ERP. These premature impulses were introduced after every tenth pacing impulse. Membrane responsiveness was determined by plotting the Vmax of these premature impulses against the membrane potentials from which they were evoked. Conduction between Purkinje fiber and ventricular muscle (PF-VM) was determined by measuring the time intervals from the start of the action potential in the Purkinje fiber to the start of the action potential in ventricular muscle. Data from ventricular muscle action potential parameters have been omitted from the results because P-M conduction block was induced by bupivacaine beginning at 3 µg/ml. Therefore, the ventricular action potentials were used primarily for determination of Purkinje-ventricular muscle conduction time.

The first experimental study (study I) consisted of superfusion of lidocaine or bupivacaine in a random-

ized fashion in ten separate preparations for each agent after a 60-minute equilibration period. In addition, a set of ten placebo experiments were included to determine changes that might occur during the 3-hour time period. The tissue preparations were exposed to concentrations of 1, 3, and 5 μ g/ml (3.5, 10, and 17×10^{-6} M) of bupivacaine or 5, 10, and 20 $\mu g/ml$ (2.1, 4.3, and 8.5 × 10⁻⁵M) of lidocaine. The tissues were exposed to each concentration for 60 minutes. A washout period of 60 minutes followed the highest concentration of drug. Recordings were made 60 minutes after exposure to each concentration of drug. During the washout period, recordings were made at 15-minute intervals to determine the rate of recovery. Spontaneous, unpaced activity was also recorded during the contol period, 60 minutes after exposure to different concentrations of the drugs and at varying intervals during the washout periods.

The second experimental study (study II) was designed to mimic the clinical situation of a rapid intravenous injection. The concentrations chosen were based on actual arterial levels of bupivacaine and lidocaine obtained in awake dogs after the rapid intravenous administration of convulsant and supraconvulsant doses of each drug, which in the case of bupivacaine produced cardiac arrhythmias (10) and are similar to values obtained in sheep (9). Twelve tissues were equilibrated for 60 minutes in normal Tyrode's solution, during which time control measurements were made. In the bupivacaine portion of the study, six tissues were exposed to 30 µg/ml of bupivacaine for 2 minutes followed by a reduction in the bupivacaine concentration to 3 µg/ml. After 28 minutes of exposure to this intermediate concentration, the concentration of bupivacaine was lowered to $1 \mu g/ml$ for a final 30 minutes followed by a 60-minute washout period.

In the lidocaine portion of the study, six tissues were exposed to 100, 10, and 2.5 μ g/ml of lidocaine in the same fashion as in the bupivacaine portion of the study. Recordings were made before and during exposure of the tissue to these various concentrations of bupivacaine or lidocaine.

Data were analyzed by a one-way analysis of variance (ANOVA) and a Newman-Keuls test followed by a paired Student's *t*-test for differences between concentrations of the same drug and an unpaired Student's *t*-test for differences between bupivacaine and lidocaine treated preparations. A *P* value of 0.05 was considered to be statistically significant.

<u>Table 1</u>. Effects of Bupivacaine and Lidocaine on Maximum Diastolic Potential (MDP), Action Potential Amplitude (AP), and Maximal Rate of Depolarization (V max)

	MDP (-mV)	AP (mV)	V max (V/sec)
Bupivacaine	(n=10)		
Baseline	80.5 ± 1.8	113.2 ± 1.8	566 ± 22
$1 \mu g/ml$	79.4 ± 1.9	107.0 ± 1.8	$393 \pm 23*$
$3 \mu g/ml$	$74.4 \pm 1.9*$	$90.2 \pm 3.8^*$	216 ± 31*
$5 \mu g/ml$	$72.2 \pm 2.2^*$	$88.5 \pm 3.3^{*}$	$135 \pm 41^{*}$
Washout	75.1 ± 1.3	108.3 ± 1.7	435 ± 56
Lidocaine	(n=10)		
Baseline	79.4 ± 1.4	114.3 ± 1.9	536 ± 22
$5 \mu g/ml$	80.0 ± 1.3	114.8 ± 1.2	$475 \pm 30^{*}$
$10 \mu g/ml$	74.2 ± 1.4	107.2 ± 3.5	414 ± 23*
$20 \mu g/ml$	76.4 ± 2.0	$107.8 \pm 2.2^*$	$336 \pm 34^*$
Washout	74.3 ± 1.5	111.5 ± 2.7	537 ± 27

^{*}P < 0.05 compared to control.

Results

No significant change in the Purkinje fiber or ventricular muscle action potentials were observed in the ten placebo preparations during a 3-hour period.

Experimental Study I

The Purkinje fiber maximum diastolic potential (MDP) decreased from an average baseline value of 80.5 ± 1.8 mV ($\overline{X} \pm \text{SEM}$) to 72.2 ± 2.2 mV after exposure to 5 μ g/ml of bupivacaine (Table 1). In the lidocaine-treated preparations the MDP varied non-significantly from an average baseline value of 79.4 ± 1.4 mV to 76.4 ± 2.0 mV after exposure to 20μ g/ml of lidocaine (Table 1). No changes in ventricular muscle MDP were seen with either bupivacaine or lidocaine.

The Purkinje fiber action potential amplitude (AP) decreased from a baseline value of 113.2 ± 1.8 mV to 90.2 ± 3.8 and 88.5 ± 3.3 mV after exposure to 3 and 5 μ g/ml of bupivacaine, respectively (Table 1). Lidocaine (20μ g/ml) also significantly reduced AP from a baseline value of 114.3 ± 1.9 mV to 107.8 ± 2.2 mV. The percent decrease in AP produced by lidocaine was significantly less than that caused by bupivacaine.

The maximum rate of depolarization (V max) was significantly decreased at all concentrations of bupivacaine (Table 1). Lidocaine also significantly decreased V max in concentrations of 5, 10, and 20 μ g/ml. However, bupivacaine (5 μ g/ml) produced a 76% decrease in V max compared with a decrease of 37% caused by 20 μ g/ml of lidocaine, a statistically significant difference. Bupivacaine and lidocaine also significantly decreased V max in ventricular muscle cells.

<u>Table 2</u>. Effects of Bupivacaine and Lidocaine on Action Potential Duration (APD) and the Ratio of Effective Refractory Period to APD (ERP/APD)

	221 22	
	APD (msec)*	ERP/APD75†
Bupivacaine	(n=10)	
Baseline	154.6 ± 6.9	1.0 ± 0.0
$1 \mu g/ml$	$121.0 \pm 7.6^*$	$1.20 \pm 0.04^*$
$3 \mu g/ml$	$110.3 \pm 10.9^*$	$1.41 \pm 0.08*$
$5 \mu g/ml$	138.1 ± 8.8	$1.36 \pm 0.09*$
Washout	128.0 ± 7.2	1.17 ± 0.06
Lidocaine	(n=10)	
Baseline	146.0 ± 9.2	1.0 ± 0.1
5 μg/ml	$119.6 \pm 8.2^*$	$1.19 \pm 0.05^*$
$10 \mu g/ml$	$115.1 \pm 6.6^*$	$1.19 \pm 0.04*$
20 μg/ml	$112.5 \pm 5.7^*$	$1.21 \pm 0.04*$
Washout	134.5 ± 6.6	1.05 ± 0.02

 $^*P < 0.05$ compared to control; action potential duration measured at 50% of repolarization

†APD₇₅ was used for this ratio because the action potential evoked for determining ERP arose closest to this level of repolarization giving control values of near unity.

The duration of the action potential at 50% of repolarization (APD₅₀) was significantly shortened by 1 and 3 μ g/ml of bupivacaine (Table 2). However, at 5 μ g/ml of bupivacaine the APD₅₀ returned toward the baseline value (Table 2). Lidocaine caused significant dose-dependent shortening of APD₅₀ (Table 2).

Both local anesthetics increased the ratio of the effective refractory period (ERP) to the APD at 75% repolarization (APD₇₅). Lidocaine also caused a significant increase of approximately 20% in the ERP/APD at all concentrations, as did bupivacaine, which increased the ERP/APD 36–41% at 3–5 μ g/ml (Table 2).

Membrane responsiveness was markedly decreased by bupivacaine and lidocaine at concentrations of 3 and 20 μ g/ml, respectively (Fig. 1). Although both anesthetics decreased membrane responsiveness, the depressant effect of bupivacaine was significantly greater than that of lidocaine (Fig. 1).

A progressive increase in conduction time from Purkinje fibers to ventricular muscle (P–M) was seen with increasing concentrations of both drugs. Bupivacaine (1 μ g/ml) caused a significant 102% prolongation of P–M conduction time (Table 3). At a concentration of 3 μ g/ml, bupivacaine also caused P–M conduction block in 90% of the preparations. At 5 μ g/ml bupivacaine, P–M conduction block occurred in 100% of the preparations.

Lidocaine also produced a significant concentration-related increase in P–M conduction time. However, at the highest concentration of lidocaine (20 μ g/ml, P–M conduction time significantly increased

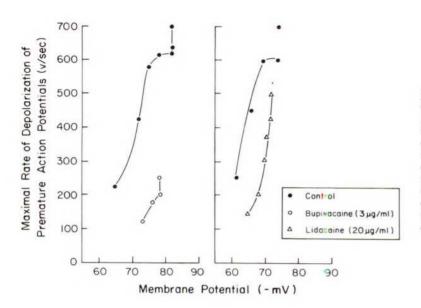


Figure 1. Membrane responsiveness of Purkinje fibers exposed to either bupivacaine (3 μ g/ml) or lidocaine (20 μ g/ml). The maximal rate of depolarization of premature action potentials evoked during repolarization of every tenth beat are plotted against the respective membrane potential from which they arose. Bupivacaine (3 μ g/ml) was significantly more potent in depressing membrane responsiveness than was lidocaine (20 μ g/ml). This is a representative result from one experiment. The multiple control points at the lowest membrane potentials indicate the frequency-dependent variability during diastole.

<u>Table 3</u>. Effects of Bupivacaine and Lidocaine on Purkinje Fiber-Ventricular Muscle Conduction Time and the Rate of Automaticity

	Purkinje-Muscle	
	Conduction	Rate
	Time (msec)	(beats/min)
Bupivacaine		
Baseline	10.5 ± 1.4	86.4 ± 13.2
$1 \mu g/ml$	$21.3 \pm 4.8^*$	51.6 ± 8.4
$3 \mu g/ml$	9 of 10 block	$33.6 \pm 9.5^*$
$5 \mu g/ml$	10 of 10 block	$31.2 \pm 9.5^*$
Washout	21.3 ± 4.5	65.4 ± 15.0
Lidocaine		
Baseline	11.5 ± 1.9	86.4 ± 16.8
$5 \mu g/ml$	$16.8 \pm 2.4^*$	43.8 ± 10.8
$10 \mu g/ml$	$16.9 \pm 3.2*$	41.4 ± 1 L4
20 μg/ml	$18.02 \pm 2.5^*$	34.2 ± 12.6*
	(1 of 10 block)	
Washout	11.88 ± 2.9	81.6 ± 10.8

^{*}P < 0.05 compared to control

only 56%. Only one preparation showed P–M conduction block after exposure to 20 μ g/ml of lidocaine.

Both agents produced a concentration-related decrease in the rate of spontaneous depolarization (automaticity). Rate decreased significantly from a baseline value of 86.4 ± 16.8 to 34.2 ± 12.6 beats/min after exposure to $20 \mu g/ml$ of lidocaine (Table 3). Similarly, bupivacaine reduced spontaneous activity significantly from a baseline rate of 86.4 ± 13.2 to 31.2 ± 9.6 beats/min at $5 \mu g/ml$ (Table 3).

Experimental Study II

Immediately after exposure of the preparation to 30

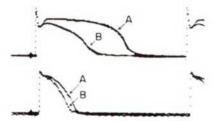


Figure 2. Effects of bupivacaine on transmembrane action potentials of rabbit Purkinje fiber (top) and ventricular muscle cells (bottom). (A) Control; (B) 2 minutes after start of bupivacaine 30 μg/ml superfusion. Preparation was constantly driven at 2.5 Hz.

μg/ml of bupivacaine, a marked decrease in action potential amplitude and duration was observed (Fig. 2). Subsequently, a progressive increase in P-M conduction time was noted until complete P-M conduction block occurred. Finally, the Purkinje fiber became inexcitable and failed to respond to a stimulus that was twice threshold. After 2 minutes, the concentration of bupivacaine was reduced to 3 µg/ml and after an additional 28 minutes, the concentration was lowered to 1 μ g/ml. After 30 minutes of exposure to this concentration, the preparation was bathed with drug-free solution for 60 minutes. An average of 18.2 ± 3.2 minutes was required for complete recovery of Purkinje fiber excitability after initial exposure to 30 μg/ml of bupivacaine. Complete recovery of P-M conduction took place in 47.8 ± 5.1 minutes (Table 4).

Lidocaine produced a similar pattern of decrease in height and duration of the action potential, followed by P–M conduction delay and block in four of the six preparations, and Purkinje fiber inexcitability in two of six preparations. However, recovery time was

<u>Table 4</u>. Duration of Bupivacaine- and Lidocaine-Induced Purkinje Fiber Inexcitability and Purkinje Fiber-Ventricular Muscle Conduction Block

	PF inexcitability* (min)	PF-VM conductior block† (min)	
Bupivacaine	18.2 ± 3.2 $(n = 6)$	47.8 ± 5.1 $(n = 6)$	
Lidocaine	3.5 ± 1.5 (n = 2 of 6)	5.8 ± 2.3 (n = 4 of 6)	

^{*}P < 0.05 for lidocaine vs bupivacaine. †P < 0.01 for lidocaine vs bupivacaine.

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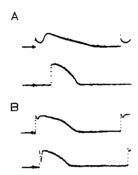
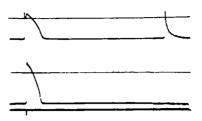


Figure 3. Notching in Purkinje fiber (top) and ventricular muscle (bottom) action potentials. (A) After 2 minutes exposure to 30 μ g/ml and subsequently 9 minutes exposure to 3 μ g/ml bupivacaine. (B) Same cells after an additional 13 minutes exposure to 3 μ g/ml bupivacaine.

significantly more rapid with lidocaine than with bupivacaine. Normal Purkinje fiber excitability recovered in 3.5 ± 1.5 minutes and P–M conduction was reestablished in 5.8 ± 2.3 minutes (Table 4).

Marked differences in the contour of the action potential were also seen with the two anesthetics. After exposure of the preparation to high concentrations of both agents, action potential amplitude and duration significantly decreased with both drugs. In addition, bupivacaine but not lidocaine produced a peculiar notching between phase 1 and 2 of the Purkinje fiber and ventricular muscle action potential (Fig. 3). The action potential showed a slow phase 0 depolarization followed by a marked phase 1 inactivation. This, in turn, was followed by a slow and somewhat delayed secondary depolarization and finally by the characteristic slow repolarization phase. On occasion the notching effect deteriorated into an alternans between a notched action potential and an action potential consisting only of a phase 0 depolarization followed by a phase 1 exponential repolarization back to the resting potential (Fig. 4).

To determine whether this peculiar action potential was simply a stimulus-induced artifact, stimulation was temporarily terminated and spontaneously generated action potentials were recorded. These



<u>Figure 4</u>. Bupivacaine-induced alternans between "notched" Purkinje fiber action potential and an action potential consisting of phases 0 and 1 which did not conduct to the ventricular muscle.

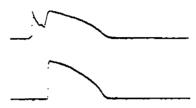
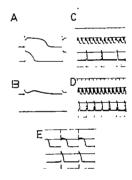


Figure 5. Notching in Purkinje fiber action potential (top) in spontaneously firing preparation at bupivacaine concentrations of $10 \mu g/ml$. "Notching" effect was usually transient lasting about 10 minutes and observed after superfusion of $30 \mu g/ml$ and during subsequent superfusion with $3 \mu g/ml$.



<u>Figure 6</u>. Effects of bupivacaine on Purkinje fiber (top) and ventricular muscle (bottom) action potentials. (A) Predrug. (B) During exposure to 30 μ g/ml (notching and P–M block). (C) 8 minutes into superfusion with 3 μ g/ml (4:1 P–M conduction). (D) 12 minutes into superfusion with 3 μ g/ml (2:1 P–M conduction). (E) 30 minutes into superfusion with 1 μ g/ml. The preparation was continuously paced at 2.5 Hz.

spontaneous Purkinje fiber and ventricular muscle action potentials also showed this notching between phase 1 and 2 (Fig. 5). However, this abnormal action potential was only seen in preparations exposed to bupivacaine. As the concentration of bupivacaine was reduced and ultimately eliminated from the bath, the action potential gradually returned to its normal contour (Fig. 6).

In addition, in several experiments premature depolarizations were observed in Purkinje fiber action potentials. These premature depolarizations tended to occur during exposure to high concentrations of bupivacaine, when conduction from the Purkinje fiber to the ventricular muscle was markedly pro-

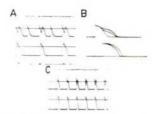


Figure 7. Bupivacaine-induced premature depolarization and anomalous prolongation of Purkinje fiber (PF) APD. (A) Premature Purkinje fiber action potentials apparent only when ventricular muscle action potentials were present. (B) Three consecutive recordings demonstrating various PF APD prolongations apparently induced by the electrotonic effects of a markedly delayed ventricular action potential. (C) Initiation of stimulation at 2:1 PF excitation—as time progressed and muscle delay increased, the secondary depolarization became more prominent.

longed (Fig. 7). These effects were not seen with lidocaine.

Discussion

Bupivacaine but not lidocaine has been shown to precipitate ventricular arrhythmias in various animal species (8–11). These studies in animals suggest that the development of severe ventricular arrhythmias may be responsible for the cases of sudden cardiovascular collapse which have been reported after the accidental intravenous injection of bupivacaine.

Few studies are available to determine the mechanism responsible for the arrhythmogenic activity of bupivacaine. Clarkson and Hondeghem (12,13), using a Hepes buffer, found that both lidocaine and bupivacaine caused a rapid decrease in V max in an isolated guinea pig papillary muscle preparation. The decrease in V max was rate- and dose-dependent. At a stimulation rate of 150 beats/min, the same stimulation rate employed in the current study, 1 µg/ml bupivacaine produced approximately a 60% decrease in V max compared to an approximate decrease of 20% after the application of 10 μ g/ml of lidocaire. Lynch, using a bicarbonate buffer solution, also demonstrated a rate and dose-dependent depression in V max of guinea pig papillary muscles (14). However, the decrease in V max at 150 beats/min was approximately 25–50% with concentrations of 1–3 μ g/ml of bupivacaine and 15% with a concentration of 10 μ g/ml of lidocaine.

In the present investigation, employing a bicarbonate buffered solution, both bupivacaine and lidocaine significantly decreased \dot{V} max in Purkinje fibers of rabbits in a dose-related fashion. At a stimulation rate of 150 beats/min, 1–5 μ g/ml bupivacaine caused a 30–76% decrease in \dot{V} max compared to a decrease of 11–37% produced by 5–20 μ g/ml lidocaine. Thus the

results of the current study are quantitatively similar to those of Lynch.

Clarkson and Hondeghem (13) also reported that 1 μ g/ml of bupivacaine caused a significant depression of \dot{V} max at stimulation rates of 20–150 beats/min, while no significant effect was observed with 10 μ g/ml of lidocaine at the lower stimulation rates. The present study did not evaluate the effects of lidocaine and bupivacaine at various stimulation rates.

Clarkson and Hondeghem (13) also reported a significant difference between bupivacaine and lidocaine in the rate of recovery from drug-induced block of sodium channels (bupivacaine, t = 1557 msec; lidocaine, t = 153.8 msec). In the present study recovery of sodium channel block was not determined. However, it was interesting to note that bupivacaine caused PF-VM conduction block in 90–100% of the preparations at concentrations of 3–5 μg/ml, while conduction block was only observed in one experiment with lidocaine at a concentration of 20 μg/ml. The region of the Purkinje fiber-ventricular muscle junction has been described by Wit (17) as an area that is sensitive to the "local anesthetic" effects of antiarrhythmic agents and, as seen in our data, the toxic effects of certain local anesthetic agents. Mendez, Mueller and Urguiaga (18) also showed that the PF-VM junction is highly sensitive to elevations in extracellular potassium resulting in block of orthodromic action potential propagation while still allowing antidromic propagation. In the current study an approximately 10-fold difference in the recovery time from PF-VM block was observed with the two local anesthetics. In addition, PF inexcitability occurred significantly more often in the bupivacaine-treated than in the lidocaine-treated preparation and recovery of PF excitability was significantly more rapid in the lidocaine-treated preparations. This difference in recovery times may be related to the greater lipid solubility and protein binding of bupivacaine, which would tend to decrease the rate of washout from cardiac tissue. In this regard Reiz and Nath (19) have reported a slower washout of bupivacaine from the heart as compared to lidocaine.

Cardiac tachyarrhythmias may be initiated by alterations in impulse generation, conduction, or both (20–22). Tachyarrhythmias due to an increase in the rate of impulse generation or automaticity may occur because of 1) depolarization of the maximum diastolic potential, 2) hyperpolarization of the threshold potential, 3) increase in the rate of phase 4 depolarization, or 4) a combination of factors 1–3. In this study bupivacaine caused a significant depolarization of the resting membrane potential. However, bupivacaine decreased the rate of the slow depolarization phase in

spontaneously beating preparations. Thus, it appears unlikely that bupivacaine-induced tachyarrhythmias are related to an increased rate of impulse generation.

On the other hand, a decrease in the rate of impulse conduction may predispose to the formation of reentrant type of arrhythmias. Factors responsible for reentrant arrhythmias include 1) depolarization of the MDP, 2) decrease in V max, 3) PF-VM conduction block, and 4) inhomogeneous alterations in APD (20-22). Bupivacaine was associated with all four conditions. Bupivacaine caused depolarization of MDP, decreased V max, produced PF-VM conduction block and markedly altered APD. In contrast, lidocaine did not significantly alter MDP and was significantly less potent than bupivacaine in terms of altering V max, APD, PF-VM conduction, and membrane responsiveness. The arrhythmogenic nature of bupivacaine was observed in several experiments in which premature action potentials were seen in the Purkinje fiber during exposure to high concentrations of the drug. Thus, the results of this study indicate that bupivacaine, but not lidocaine, is capable of inducing a reentrant type of tachyarrhythmia.

The marked depression of V max supports the conclusion of Clarkson and Hondeghem (13) that bupivacaine may block sodium channels in cardiac membrane. In addition, the peculiar notching of the action potential between phase 1 and phase 2 after exposure of the Purkinje fiber-ventricular muscle preparations to a high concentration of bupivacaine (30 μ g/ml) may be related to enhanced sodium inactivation or, perhaps, inhibition of the slow inward calcium currents. There is an inward flow of calcium current during the plateau phase of the action potential. Inhibition of these calcium currents could lead to an exaggeration of the sodium inactivation phase and a decrease in the amplitude of the action potential as was seen in these studies. Recently, Lynch reported that bupivacaine depressed high potassium, isoproterenol-induced, slow inward current action potentials at concentrations similar to those used in this study (14). Other studies also are suggestive of an interaction of local anesthetics and calcium in cardiac tissue. For example, slow channel blockade by tetracaine was reported by Carmeliet (23). In addition blockade of intracellular release of calcium by tetracaine in isolated sarcoplasmic reticulum preparations and intact Purkinje fiber have also been reported (24,25).

The concentrations of lidocaine and bupivacaine employed in the second part of these studies were based on blood concentrations of these two agents measured in animals given toxic intravenous doses of these drugs (10). However, the solutions in our in

vitro studies were protein free. Bupivacaine binds to plasma proteins to a significantly greater extent than does lidocaine, but at high blood concentrations the plasma protein binding of both agents is markedly decreased. For example, 1 µg/ml free bupivacaine corresponds to a whole blood concentration of approximately 5 μ g/ml. However, a concentration of 30 μg/ml free bupivacaine would be present at a whole blood concentration of approximately 60 µg/ml in blood (26,27). Whole blood concentrations of >60 μ g/ml bupivacaine have been reported in animals (9). Also, in certain patients, including parturients, several factors are altered that may increase the free concentration of bupivacaine (26,28): 1) a decrease in the concentration of serum albumin; 2) a decrease in the alpha, acid glycoproteins binding sites, and 3) an increase in the concentration of non-esterified fatty acids that could compete for binding sites.

Therefore, although the concentration of bupivacaine (30 μ g/ml) and lidocaine (100 μ g/ml) are admittedly high, the differential electrophysiologic effects of these two local anesthetics may be clinically relevant in terms of elucidating the etiology of bupivacaine-induced arrhythmias. Furthermore, the Purkinje fiber–ventricular muscle conduction block that may be primarly responsible for initiation of a reentrant type of arrhythmia also occurred at concentrations of 3–5 μ g/ml of bupivacaine, which can be easily achieved after an accidental intravascular injection in humans.

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Laser-Induced Pain for Evaluation of Local Analgesia:

A Comparison of Topical Application (EMLA) and Local Injection (Lidocaine)

Lars Arendt-Nielsen, PhD, and Peter Bjerring, MD

ARENDT-NIELSEN L, BJERRING P. Laser-induced pain for evaluation of local analgesia: a comparison of topical application (EMLA) and local injection (lidocaine). Anesth Analg 1988;67:115–23.

High-energy lasers are suitable for experimental pain stimulation because they selectively activate the polymodal nociceptors. Argon laser light penetrates deep into the skin and makes this laser type preferable for simulating pain arising from surgical skin incisions. Short argon laser pulses were applied to the skin and three parameters were quantified before and during analgesia; sensory threshold, pain threshold, and the pain-related cortical response (latency and amplitude). Determination of sensory and pain thresholds made it possible to distinguish between two levels of analgesia; the pain block, where no pain was felt but other sensations were still perceived; and total sensory block, where the laser stimulus elicited no sensations of any type. The analgetic effects of cutaneous injections of lidocaine and topical application of EMLA (eutectic mixture of local anesthetics) cream were evaluated and compared by means of the introduced parameters. Lidocaine produced total sensory block almost immediately after injection, which was associated with the absence of cortical response to cutaneous laser stimulation. When the EMLA cream was applied for 15 minutes, both sensory and pain thresholds increased. During the next 30 minutes after removal of the cream, the

thresholds increased further. The increase in analgetic effect after removal of the cream was studied using different times (15, 30, 60, 80, 100, and 120 minutes) for topical EMLA cream application. Total sensory block was reached 20 minutes after removal of application for 80 minutes or immediately after removal of the cream after it was applied for 100 or 120 minutes. Pain block was achieved 30 minutes after removal of cream applied for 30 minutes, 15 minutes after removal of cream applied for 60 minutes, and immediately after applications for 80, 100, or 120 minutes. During the period of increasing and decreasing analgesia, cortical responses were recorded. Changes in amplitude and latency reflected the changes in perception (intensity and modality) to laser stimuli. In some cases a sensation of local warmth was perceived when pain perception was absent. The sensation of local warmth was accompanied by cortical deflections with a latency of 600-800 ms from stimulus onset, which was 200-300 ms later then the cortical deflections related to pain perception. Thresholds and cortical responses to argon laser stimuli were affected by minor changes in sensitivity of the nociceptors in human skin and were found to be suitable parameters for quantitative evaluations and comparisons of dermal analgesics.

Key Words: PAIN, EXPERIMENTAL—Laser-produced. ANESTHETICS, LOCAL—topical.

Injectable solutions of lidocaine are widely used to provide local anesthesia for superficial, minor operative procedures. Lidocaine acts directly on nerve membranes by blocking sodium conductance in the nerve membrane during depolarization. For skin analgesia, lidocaine is usually infiltrated intra- and subdermally, where it is distributed diffusely through the tissues and directly affects receptors and nerve

endings in the area. The injection is often accompanied by a significant discomfort or pain.

A topical preparation of local anesthetics that can be applied to the skin without discomfort and that alleviates pain from needle punctures would be most helpful to both patient and anesthetist. Indeed, many attempts have been made to obtain suitable formulations of effective topical anesthetics. The main problem has been poor penetration through the intact epidermis. Mixtures of lidocaine and prilocaine crystals form an eutectic mixture that, in an oil-in-water emulsion, produce droplets of approximately 80% active local anesthetic substance. This emulsion (Eutectic Mixture of Local Anesthetics—EMLA, Astra

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AB, Sweden) penetrates intact skin and blocks pain produced by pinpricks. The eutectic mixture is especially useful in children before venipuncture (1–5).

Evaluation of the anesthetic effect of epicutaneous EMLA application and conventional lidocaine infiltration have traditionally been based on subjective reports in which patients estimate pain sensation verbally or by use of visually graded scales.

The aim of the present study was to use a quantitative method to 1) compare two methods for obtaining dermal analgesia (topical EMLA cream and lidocaine infiltration); 2) determine the effects of various durations of application of EMLA; and 3) measure the duration of analgesia produced.

We selectively stimulated cutaneous nociceptors by high-energy argon laser pulses and measured the sensation and pain thresholds and pain-related cortical evoked responses associated with various levels of analgesia.

Methods

Stimulation

The output from an argon laser (Lexel Aurora 50, Cooper Medical, USA) was transmitted via a quartz fiber to a handpiece with adjustable beam diameter (0.4 to 6 mm). The laser was operated in TEM_{00} mode. Output power could be adjusted from 0.005 to 2.9 W. The wavelengths were 0.488 μ m (blue) and 0.515 μ m (green). An external laser power meter (Ophir, Israel) was used to measure the dissipated output power. A continuous low energy beam (0.005 W) from the argon lasar visualized the stimulation site. The laser stimulus had a duration of 200 ms and the laser beam diameter was kept constant at 3 mm by a spacer between the fiber optics and the skin surface.

The laser stimulus was applied to the dorsum (C7 dermatome) of the left hand in a 6 cm² test area. The test area was encircled by ink to ensure that the same area was used in consecutive experiments. Repeated stimulation at identical points within the area was avoided by dividing the test area into small sectors that were sequentially stimulated to exclude any effect of receptor fatigue or receptor sensitization. The intervals between stimuli were randomized with a mean of 30 seconds (range 10 to 30 seconds). The maximal laser intensity applied to the skin was 2.4 W. Intensities above this level caused minor superficial skin burns and this level was therefore defined as skin destruction level (SDL). Two levels of analgesia were defined: blockade of pain and total sensory blockade. The pain blockade was defined as being

<u>Table 1</u>. Seven-Point Scale for Perception of Argon Laser Stimuli*

Perception	Scale	Abbreviation	Rating
Very intense pinprick and burning after sensation	6	VIPP/BS	Very strong pain
Intense pinprick	5	IPP	Strong pain
Sharp distinct pinprick	4	SDPP	Moderate pain
Distinct pinprick	3	DPP	Threshold of pain
Weak pinprick, warmth	2	PP/W	Prepain
Faint pinprick, slight touch, faint warmth	1	PP/T/W	Threshold of sensation
No sensation	0	NS	

^{*200} ms duration, 3 mm beam diameter.

present when argon laser stimulus pulses up to SDL were not perceived as painful, whereas sensations of warmth, touch or nonpainful pinprick could still be perceived. Total sensory blockade was defined when nothing was perceived when stimuli with intensities up to SDL were applied.

Threshold Determination

The declaration of Helsinki was respected and informed consent was obtained from all volunteers. During the experiment the volunteers rested comfortably and wore protective goggles. To standardize the acoustical perception and avoid any perception synchronized to the stimulus, white noise was given through earphones.

Skin temperature on the dorsum of the hand was monitored by a thermocouple fixed to the skin surface with transparent tape. Stimuli were applied when the skin temperature on the dorsum of the hand was $33 \pm 2^{\circ}$ C.

The thresholds were calculated as the mean of five ascending and five descending series of stimulations. The sensory threshold was defined as rating 1 and the pain threshold was defined as rating 3 on a seven-point scale (Table 1).

The influence of skin temperature, skin thickness, and skin reflectance on argon laser thresholds has been described by Arendt-Nielsen and Bjerring (6).

Reaction Time

A counter (1/1000-second resolution) was triggered by the onset of stimulus. The counter was stopped by a small thumb switch. Each reaction time was based on 20 stimulations. The intervals between stimulations were random with a mean of 30 seconds (range 15 to 45).

Recording of Cortical Responses

Cortical responses were recorded with a platinum needle electrode (Disa 25CO4) inserted subcutaneously over the vertex. A reference surface electrode was applied to the earlobe.

The EEG was filtered (0.5–200 Hz) and amplified 200,000 times (Disa 5CO1). A microcomputer system was triggered by stimulus onset. One-second strips of EEG activity were recorded and 32 to 128 successive recordings were averaged.

Statistical Analysis

Statistical evaluation of the results was performed by Wilcoxon's test. Statistical significance was accepted to a 5% level.

Analgesia

EMLA and placebo. The EMLA cream consists of an oil-in-water emulsion of an eutectic mixture of lidocaine base (25 mg/ml) and prilocaine base (25 mg/ml). A placebo cream without active substances was prepared and marked similar to EMLA cream. EMLA and placebo were supplied in identical aluminum tubes. The tubes were marked in a double-blind manner. A thick layer of the cream (2 g) was applied to a 10-cm² skin area on the dorsum of the left hand (C7 dermatome) under an impermeable plastic occlusive film. The test area was in the center of the area of application.

Lidocaine and placebo. Identical values (2 ml) of lidocaine (1%) and placebo (NaCl 0.9%) were injected intradermally on the dorsum of the left hand (C7 dermatome) with a 28-gauge needle into a 10-cm² skin area. The test area was in the center of the area of injection. Lidocaine and placebo were supplied in identical vials and marked in a double-blind manner.

Experiment 1

Analgetic Effects of Lidocaine Infiltration, EMLA Cream Application (60 and 120 minutes), and Placebo Evaluated by Threshold Determination and Pain-Related Cortical Responses

In this experiment the efficiency of EMLA cream was compared with that of conventional lidocaine

infiltration. Placebo analgetics were prepared to determine if thresholds were altered by the cream base or by the injection itself.

Subjects. Twelve healthy volunteers (6 men, mean age 27 years, range 24–33, and 6 women, mean age 25 years, range 23–27) were tested in random order on six consecutive days:

Day 1—EMLA cream applied for 60 minutes,

Day 2—EMLA cream applied for 120 minutes,

Day 3-placebo cream applied for 60 minutes,

Day 4—placebo cream applied for 120 minutes,

Day 5—lidocaine injected, and

Day 6—placebo injected.

Sensory and pain thresholds before and after lidocaine or placebo injection and EMLA or placebo application. The thresholds were determined before and after infiltration or cream application. The thresholds were measured 8 minutes after injection of lidocaine or placebo and after 60 or 120 minutes of application of EMLA.

Pain-related cortical responses before and after lidocaine or placebo injection and EMLA or placebo application. Cortical responses were measured before and after infiltration or cream application. The responses were measured 8 minutes after lidocaine or placebo infiltration and again after cream application for 60 or 120 minutes. The laser stimulus intensity was adjusted throughout to the subjective rating 4, measured before infiltration or cream application.

Experiment 2

Curation of Analgetic Effect of EMLA Cream Applied for 15, 30, 60, 80, 100, and 120 Minutes Evaluated by the Thresholds

In the previous experiment the thresholds were measured several times after removal of the cream. It was observed that the thresholds increased during consecutive measurements and the following experiment was designed to study this phenomenon systematically.

Subjects. Ten healthy volunteers (six men, mean age 26 years, range 22–35, and four women, mean age 28 years, range 24–33) was tested on 6 consecutive days with EMLA cream applied for either 5, 30, 60, 80, 100, or 120 minutes. The application times were chosen in random order on the different days.

Sensory and pain thresholds after EMLA application—a kinetic study. The thresholds were initially deter-

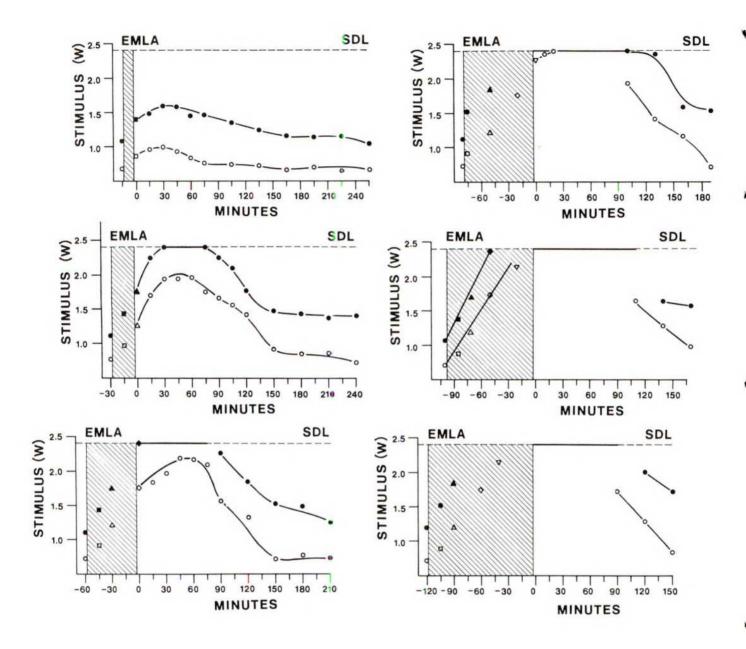


Figure 1. Sensory (o) and pain (•) thresholds determined after 15, 30, 60, 80, 100, and 120 minutes of EMLA cream application (hatched area) on the dorsum of the hand. The thresholds to argon laser pulses (200 ms duration, 3 mm beam diameter) were determined every 15–30 minutes after the EMLA cream was removed. The mean threshold values in ten subjects (mean age 27 years, range 22–35) were calculated. Skin destruction level (SDL) was reached for laser impulse above 2.4 W. Intensities above this level induced minor superficial skin burns.

mined before application of EMLA cream. Each 15th–30th minute (for actual intervals see Fig. 1) after the EMLA cream was removed, the thresholds were determined. The total duration of the experiment was 270 minutes. The criteria for analgetic efficiency were pain block and total sensory block, as previously defined.

Experiment 3

Duration of Analgetic Effect of EMLA Cream Applied for 30 Minutes Evaluated by Pain-Related Cortical Responses

To study the sensitivity of pain-related cortical responses to various levels of analgesia, the 30-minute application time was selected because with it, pain block could be selectively produced (Fig. 2). The cortical projection of nonpainful sensation was compared to the threshold findings.

Subjects. The study included six healthy volunteers (four men, mean age 27 years, range 23–33, and two women, 28 and 31 years old).

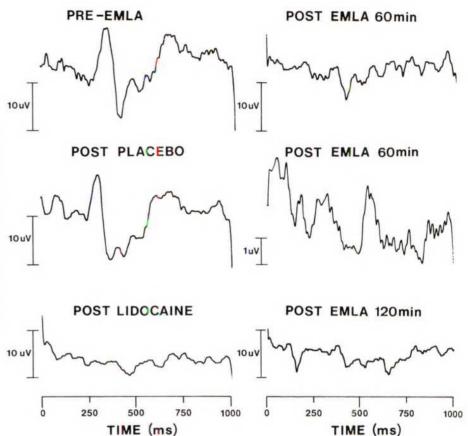


Figure 2. Cortical responses evoked by thermal argon laser pulses (200 ms duration, 3 mm beam diameter) applied to the dorsum of the hand (woman, age 27). The responses were recorded from vertex to earlobe. The preanalgetic response was similar to the placebeo response. The postanalgetic responses were recorded after lidocaine injection, after 60 minutes of EMLA cream application, and after 120 minutes of EMLA cream application. Two responses (notice different vertical axis) recorded after 60 minutes of EMLA application are shown. One response corresponded to a weak pinprick (right, top), and the other, (second from right, top) corresponded to the sensation of warmth (woman, age 25).

Pain-related cortical responses after 30-minute EMLA application. The argon laser stimulus intensity used was 20% above the pain threshold determined immediately after removal of the EMLA cream. The cortical responses were recorded every 15 minutes for 150 minutes.

Results

Sensory and Pain Thresholds Before and After Lidocaine or Placebo Infiltrations and EMLA or Placebo Application

The thresholds before and after injection of lidocaine or placebo are given in Table 2. The thresholds after lidocaine infiltration increased significantly. In 2 of 12 subjects the laser stimuli after injection of lidocaine were perceived as nonpainful pinpricks (pain blockade only). In the other ten subjects nothing was perceived (total sensory blockade). There was a statistically nonsignificant tendency for thresholds to increase slightly after the placebo injections.

The thresholds after EMLA or placebo applications are given in Table 2. When EMLA cream was applied for 60 minutes, total sensory blockade was obtained

in 3 of 12 subjects. Placebo cream applied for 60 minutes did not change the thresholds significantly, though there was a tendency for thresholds to increase slightly.

EMLA cream applied for 120 minutes produced total sensory block in all cases, whereas the placebo cream did not change the thresholds significantly.

The intraindividual variations (for the six consecutive determinations) in thresholds determined before analgesia were 9.92% (coefficient of variation) for the sensory threshold and 5.77% (coefficient of variation) for the pain threshold (12 subjects).

The intraindividual variations in thresholds to argon laser stimuli recently described by Arendt-Nielsen and Bjerring (6) are similar (9.3 and 4.3%, respectively) to results obtained in the present study.

Test of Lidocaine or Placebo and EMLA or Placebo by Cortical Evoked Responses

The stimulus intensity used to elicit cortical responses was the same before and after injection or cream application. After lidocaine injection or 120 minutes of EMLA cream application, total sensory blockade was obtained in all cases (7) and no cortical responses

Table 2. Sensory and Pain Thresholds*

	Sensory Thresholds (W)		Pain Thresholds (W)	
	Before	After	Before	After
Lidocaine injection	0.75 ± 0.31	$2.10 \pm 0.09 \ (n=2) \text{ TSB } (n=10)$	1.37 ± 0.45	PB $(n = 2)$ TSB $(n = 10)$
Placebo injection	0.72 ± 0.25	0.80 ± 0.13	1.21 ± 0.42	1.30 ± 0.37
60 min EMLA cream	0.79 ± 0.40	$2.06 \pm 0.07 (n=9) \text{ TSB } (n=3)$	1.36 ± 0.47	PB $(n = 9)$ TSB $(n = 3)$
60 min placebo cream	0.66 ± 0.25	0.75 ± 0.33	1.29 ± 0.33	1.39 ± 0.36
120 min EMLA cream	0.83 ± 0.28	TSB	1.38 ± 0.43	TSB
120 min placebo cream	0.75 ± 0.27	0.80 ± 0.30	1.29 ± 0.29	1.38 ± 0.29

^{*}Determined on the dorsum of the hand (C7-dermatome) in 12 subjects (mean age 26 years, range 23–33). Total sensory blockade (TSB) was reached when no sensations followed a laser stimulus. Painblock (PB) was reached when no pain was perceived. The maximal laser intensity was 2.4 W. Intensities above this level caused minor superficial skin burns. The mean and SEM are given.

were detected (Fig. 2). After 60 minutes of EMLA application, pain blockade was obtained in 9 of 12 subjects and total sensory blockade in 3 subjects. The prepain sensations were described as either nonpainful pinpricks or as a feeling of warmth. Characteristic cortical responses were recorded with these different prepain sensations (Fig. 2). The sensation of warmth was accompanied by a late cortical response, with a major negative deflection 640 ± 112 ms after stimulus onset. This was a shift in latency of the cortical response of 293 ± 51 ms compared to the major pin prick-related negative deflection recorded before analgesia. The reaction time was measured before each recording and a delay of 279 ± 88 ms was found.

Duration of Analgetic Effect of EMLA Cream Applied for 15, 30, 60, 80, 100, and 120 Minutes Evaluated by the Thresholds

The kinetics of the onset, duration, and decrease of analgesia was studied after various application times of EMLA cream. The results are shown in Fig. 1.

15 minutes. Application of EMLA cream for 15 minutes resulted in a significant increase of both sensory and pain thresholds. The maximal effect was a 40% increase in sensory threshold and a 44% increase in pain threshold, both 30 minutes after removal of the cream. Both thresholds decreased slowly toward normal values. No pain blockades or total sensory blockades were obtained.

30 minutes. When EMLA cream was removed from the skin surface after 30 minutes, the sensory threshold continued to increase and reached a maximum of 150% of preanalgetic values 60 minutes after removal of the cream. The pain threshold was elevated 65% immediately after removal of the cream; pain blockade occurred 30 minutes later and lasted 60 minutes.

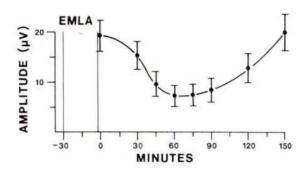
60 minutes. After a 60-minute application, analgesia was not total immediately after removal of the cream. However, after an additional 15 minutes, pain block was obtained and persisted for 75 minutes. Sensory threshold reached a maximum of 197% 45 minutes after removal of the cream and returned to the baseline level 150 minutes after removal.

80 minutes. Eighty minutes of EMLA cream application gave immediate pain block when the cream was removed, and total sensory block was obtained 20 minutes later. One hundred minutes after removal of the cream, the sensory threshold was detectable again, and it reached its normal value after 190 minutes. The pain threshold reappeared under SDL 100 minutes after cream removal, but did not quite assume its initial value even after 190 minutes.

100 and 120 minutes. Both 100- and 120-minute application times resulted in total sensory block immediately after removal of EMLA cream. Sensory threshold was again detected 90–110 minutes later and the pain threshold was reached below SDL 120–140 minutes later.

Duration of Analgetic Effect of EMLA Cream Applied for 30 Minutes Evaluated by the Cortical Responses

From the previous experiment it was possible to select an application time (30 minutes) associated with pain blockade without total sensory blockade. The mean amplitude of the cortical responses decreased gradually the first 60 to 90 minutes after EMLA cream was removed (Fig. 3). After 60 to 90 minutes, the analgesia began to be less effective and the fixed stimulus intensity was perceived as being more and more painful. This increase in pain intensity was related to a corresponding increase in cortical amplitude (Fig. 3).



<u>Figure 3</u>. The mean amplitude (six volunteers, mean age 28 years, range 23–33) of the main cortical complexes monitored after EMLA cream was applied on the dorsum of the hand for 30 minutes. The argon laser impulses (200 ms duration, 3 mm beam diameter) were applied to the dorsum of the hand. The vertical bars indicate the SEM.

Discussion

Because injection of local anesthetics into the skin is a minor anesthetic maneuver frequently performed for small surgical procedures, many attempts have been made to obtain a suitable formulation for effective topical anesthesia of the skin. Previously, a major obstacle has been poor penetration of local anesthetics through intact skin, but the eutectic mixture of lidocaine base and prilocaine base (EMLA cream) has been shown to be capable of penetrating intact skin in amounts sufficient to abolish pain of pinprick (1,8). The clinical effects of EMLA have been intensively studied, especially for alleviating pain during intraveneous cannulation (2–5).

Traditional stimuli (electrical and mechanical) used in most experimental pain studies activate a nonspecific spectrum of fibers. High energy laser light, however, activates nociceptors selectively (9), and is therefore better when studying changes in the nociceptive pathway (6). This method of laser stimulation is shown in the present study to be useful for quantitative evaluations of local analgetics. The sensory and pain thresholds to laser stimuli are very sensitive for detection of changes in skin conditions and changes in receptor response characteristics.

Placebo Cream Application and Placebo Infiltration Change the Sensory and Pain Thresholds

Placebo injection. Placebo injections (NaCl 0.9%) increased thresholds slightly. The placebo injection was a painful experience and could therefore introduce an offset in the general level of sensitivity. This is in accord with findings that concurrent subacute pain increases the pain threshold to noxious electrical

stimuli (10). However, the increase in thermal thresholds could also be due to the increased water content in the skin, which increases the heat capacity.

Placebo application. Application of a placebo cream also increased the thresholds slightly, presumably because of the moisturizing effect of the cream base, which increases the water content and thus the heat capacity of the upper skin layers. This increased intracutaneous water content tends to absorb part of the laser energy and, thus, tends to increase the thresholds.

The Analgetic Effect of EMLA May Be Comparable to Lidocaine Infiltration

The analgetic efficiency of EMLA cream increased with longer application times (60 to 120 minutes); the effect after 2 hours of application was similar to local analgesia produced by conventional lidocaine infiltration. With clinical use of EMLA cream, one may anticipate a delay in onset of analgesia. In some cases, this may be unacceptable, but for venipuncture in children, minor skin surgery and laser therapy for hemangiomas the cream may be useful for elimination of painful injections.

The Analgetic Effect of EMLA Increases After Removal of the Cream

Previous studies have shown that the effect of EMLA cream evaluated by pain scores increases with increasing application time (4,8), whereas Dohlwitz and Uppfeldt (11) were not able to demonstrate any effect of prolonged application times. The manufacturer's recommended application time of 60 minutes is insufficient to produce full analgesia in normal adult skin on the dorsum of the hand. Differences in effect and onset time may be anticipated for different locations on the body because of variation in skin thickness and blood flow. However, when 15 minutes was allowed after removal of the cream, pain block was obtained. Application times of 80 minutes were necessary to obtain total sensory blockade. The total sensory blockade was obtained 40 minutes after removal of the cream. To obtain total sensory blockade immediately after removal of the cream, an application time of 100 minutes minimum is required.

With 15, 30, and 60-minute application times, the maximal effect on both the sensory and pain modalities occured after removal of the cream from the skin surface. This is similar to the findings of Evers et al.

(8) and it may indicate that a reservoir of anesthetic is located and stored in the upper skin layers during application. After the cream is removed, the diffusion to the deeper skin layers continues and the lidocaine and/or prilocaine may accumulate in different components of the lower skin layers. Selective uptake and even transport of analgetics in the nervous tissues may also be responsible for the later and less pronounced effect observed on the sensory threshold than on the pain threshold.

The results suggest new indications for the use of EMLA cream with different recommendations for application times. In the dermatologic outpatient clinic, we use EMLA cream for laser treatment of hemangiomas of the face. The patients apply the cream at home under occlusion for 1 hour, remove the cream and, while coming to the hospital, the effect increases sufficiently to abolish pain during treatment.

The Shape of Laser-Induced Pain-Related Cortical Responses Is a Sensitive Model for Evaluation of Local Analgetics

Recordings of cortical responses to experimental argon laser-induced pain have recently been described (7,12) and are found to be a sensitive method when topically applied analgetics are evaluated and compared. The amplitude of the pain-related cortical responses elicited by high energy lasers correlate, for example, with subjective pain ratings (7,13–18). The amplitudes of cortical pain-related responses are modulated by local analgetics, as reflected by trends in analgetic levels measured by changes in thresholds during the periods of increasing and decreasing analgesia.

The shape (latency and amplitude) of the cortical evoked responses provides information on 1) the reduction in pain sensitivity compared with the preanalgetic levels; and, 2) perceptual changes introduced by the analgesia. When nothing was felt, no cortical responses could be recorded, indicating that no proprioceptive, muscle, or other afferents were activated by the thermal pulses from the argon laser. When pain alleviation was complete, prepain sensations of warmth, touch and nonpainful pinpricks were still perceived. The sensation of local warmth was accompanied by a cortical response 200 to 300 ms later than the normal pain related complex.

The sensation of warmth is of special interest because lidocaine is known to block the formation and transmission of action potentials in thin unmyelinated fibers before the thicker myelinated fibers.

The sensation of warmth may be transmitted by thin unmyelinated C-fibers (19), whereas the pain of a pinprick arises from activation of nerve endings innervated by myelinated Aδ-fibers (9,20), and the sensation of warmth should, therefore, under normal conditions disappear before the pinprick sensation. Our findings thus suggest that warmth receptors, or at least part of them, may be located in a deeper dermal layer, and therefore are not reached by effective concentrations of analgesics. It is generally accepted that the main parts of the sensory nerve fibers terminate in the upper part of dermis around the papillary capillaries under the epidermal/dermal junction (21), but the anatomic position and distribution of warmth receptors have not been fully evaluated.

Conclusion

Recordings of cortical responses are often preferable to threshold determinations because the shape of the cortical response contains information on perceptual changes to the stimulus, whereas the threshold measurements mainly reflect changes in sensitivity to the stimulus. When both sensitivity changes and perceptual changes are to be studied, a combination of threshold determinations and cortical response recordings elicited by argon laser stimuli is an optimal quantitative method. High energy argon laser stimulation is recommended as a thermal stimulator in the study of local analgesia because the laser light penetrates through epidermis and reaches the deeper dermal layers where part of the receptors might be located and is, therefore, a suitable model for measurement of pain arising from surgical skin incisions.

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Esmolol Decreases the Adverse Effects of Acute Coronary Artery Occlusion on Myocardial Metabolism and Regional Myocardial Blood Flow in Dogs

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SIDI A, DAVIS RF. Esmolol and coronary artery occlusion. Anesth Analg 1988;67:124–30.

This study was designed to test the hypothesis that β adrenergic receptor blockade with esmolol would decrease the hemodynamic and myocardial metabolic impairment produced by left anterior descending coronary artery (LADa) occlusion. Twenty-three anesthetized open-crest dogs underwent direct cannulation of the LADa, its companion vein (LADv), and a distal circumflex vein (CFXv) for blood sampling. All dogs were subjected to two consecutive 15-minute periods of total LADa occlusion; group 1 (n = 11) received an infusion of esmolol (150 $\mu g \cdot kg^{-1}$ ·min⁻¹) during either occlusion period (randomly assigned) and group 2 (n = 12) received no intervention during either occlusion period. One hour of reperfusion was interpesed between the two periods of LADa occlusion. Hemodynamic measurements were made and blood was sampled from the aorta, CFXv, LADa, and LADv before and during both periods of LADa occlusion. Without esmolol infusion, LADa occlusion was associated with decreases in stroke index, coronary perfusion pressure, and left ventricular stroke work index; with esmolol infusion these hemodynamic decrements did not occur. During both LADa occlusion periods in both groups, lactate extraction became negative, i.e., there was net lactate production. Despite this, the magnitude of lactate production was less with esmolol than without it. Finally, average endocardial-to-epicardial blood flow ratio in the LAD perfusion area was decreased during each LAD occlusion period except when esmolol was infused, during which the baseline value was maintained. Thus, infusion of esmolol during temporary LADa occlusion preserved certain hemodynamic variables, preserved the ratio of endocardial-to-epicardial blood flow, and decreased the apparent magnitude of lactate production.

Key Words: HEART—coronary blood flow. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

The extent of myocardial ischemic necrosis caused by coronary artery occlusion is affected by physiologic and pharmacologic interventions, both experimentally and clinically (1). Because propranolol decreases the effect of myocardial ischemia experimentally (2) and reduces mortality from myocardial infarction during long-term oral administration clinically (3), we questioned whether transient β -blockade might decrease the effect of ischemia during intermittent periods of stress, as may occur intraoperatively during cardiac or major vascular surgical operations. Esmolol, a semiselective, β -one adrenergic receptor antag-

onist, has an extremely brief duration of action (4,5). This agent therefore could produce a transient blockade of cardiac β -receptors when the myocardium is vulnerable to ischemia as a result of increased adrenergic neural tone, increased circulating catecholamines, or altered hemodynamic variables during a surgical operation. In this study, we tested the hypothesis that such a transient β -adrenergic receptor blockade produced by esmolol would permit sustained myocardial performance while decreasing ischemic anaerobic metabolism in a canine model of acute coronary artery occlusion (6,7).

Twenty-three adult mongrel dogs of either sex, ranging in weight from 14.6 to 20.0 kg, were premedicated with an IM dose of morphine sulfate (2.5 mg/kg) given 30 minutes before anesthetic induction. Anes-

Materials and Methods

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thesia was induced with 16 mg/kg thiamylal and was maintained with a continuous infusion of α chloralose (10 mg/kg/h). For each dog, the trachea was intubated and the lungs were mechanically ventilated with an air-oxygen mixture to keep Pao₂ between 90 and 130 mm Hg and Paco, between 30 and 40 mm Hg. Catheters were introduced into the pulmonary artery (PA) and the aorta (Ao) through the femoral vein and artery to measure cardiac output (CO) (by thermodilution) and pressures. After a left fifth interspace thoracotomy, the heart was suspended in a pericardial cradle. The left ventricle (LV) was cannulated from the left atrium (LA) with a transducer-tipped catheter (Millar) to measure LV pressure and its first derivative (LV dP/dt). The left anterior descending coronary artery (LADa) was isolated proximal to the first major apical diagonal branch and loosely surrounded with a silastic ligature fashioned into a pseudo-Rummel tourniquet by using 14- to 18-gauge red rubber tubing. The exact location of the ligature was selected so that a 10- to 15-second occlusion of the LAD produced obvious cyanosis of the cardiac apex. Teflon catheters (24-gauge) were placed into the LAD distal to the ligature, into the adjacent coronary vein (LADv), and into a distal circumflex vein (CFXv) (8). The catheters were fixed in place by using a 5-0 prolene suture placed into the epicardium adjacent to the point at which the catheter entered the vessel.

Electrocardiogram (ECG) (standard lead II) and heart rate (HR) were recorded continuously; CO was measured in triplicate using 5 cc of 4°C injectate and a thermodilution CO computer (model #9520A, Edwards Laboratories). Pulmonary artery and Ao pressures (systolic, diastolic, and mean), LV end-diastolic pressure (post "A" wave), and LV dP/dt (obtained electronically) were recorded continuously by using the Millar catheter (LV) or calibrated Gould-Statham P 50 transducers (PA and Ao). Rigid, saline-filled polyethylene tubing (Cobe, Inc.), 4-feet-long, connected the PA and Ao transducers and the respective catheters. All standard transducers were calibrated with a mercury manometer and checked for drift before each measurement. The directly visualized LA was taken as the zero reference for calibration. Cardiac index (CI), stroke volume index (SVI), coronary perfusion pressure (CPP) (Ao diastolic-LV enddiastolic), left ventricular stroke work index (LVSWI), and total systemic (SVR) and pulmonary (PVR) vascular resistances were calculated from measured variables by accepted hemodynamic formulae (9).

For each experiment, two periods of total LADa occlusion were produced by tightening the previously placed ligature. After 15 minutes of total LADa

occlusion, the ligature was released and the LAD opened to restore normal perfusion for 1 hour, after which a second 15-minute period of ischemia was induced. Data were collected before and at the end of each LADa occlusion period. The dogs were arbitrarily assigned to one of two groups that were studied consecutively. In group 1 (n = 11), an esmolol infusion (150 μ g·kg⁻¹·min⁻¹) was begun before either the first or second LADa occlusion period by randomized assignment; randomization of esmolol treatment to period 1 or 2 was performed after the initial preparation as described. In group 2 (n = 12), no experimental intervention was used during either LADa occlusion period. Isoproterenol (5 μ g) was injected before LADa occlusion and the resultant HR recorded for both LADa occlusion periods in both groups so that the magnitude of any residual β blockade from an antecedent esmolol infusion could be assessed. The isoproterenol challenge was given before each LADa occlusion in both groups and the LADa was not occluded until HR had returned to the preisoproterenol value. Thus, the possible effects of esmolol (treatment, group 1) and the effects of the sequential design of the study (control, group 2) were controlled. In both groups, before and at the end of each LADa occlusion period, blood was sampled frcm the Ao, PA, LADa, LADv, and CFXv for measurement of blood gas tensions, pH, and concentrations of lactate, glucose, sodium (Na), and potassium (K) and for calculation of base excess (BE) or deficit.

For microsphere injection, an 18-gauge catheter was placed into the left atrial appendage. Approximately 1.5×10^6 (1-cc solution) 15- μ m diameter, radionuclide-labeled microspheres (isotopes of Nb, Sr, Sc, Cr, and Ce selected randomly) were injected into the LA over 20 seconds. The injecting syringe and tubing were flushed immediately with 10 ml normal saline. The reference sample was obtained by aspiration of arterial blood at a constant rate (22.9 cc/min) from the Ao by using a Harvard pump beginning 15 seconds before microsphere injection and continuing for 2 minutes. At the conclusion of each study, transmural samples of LV myocardium (approximately 2 g each) were obtained, three from normal-appearing myocardium outside the distribution of the occluded vessel and three from cyanotic myocardium within the distribution of the occluded vessel. Each sample was divided into endocardial (En) and epicardial (Ep) halves and weighed. Reference blood samples, myocardial tissue samples, injecting syringes, and associated catheters and tubing were placed into polyethylene tubes and radioactive emissions were measured by a gamma counter (model 1282, LKB Wallach) that corrected for emis-

Table 1. Hemodynamic Effects of Left Anterior Descending Coronary Artery Occlusion With and Without Esmolol

	Period 1		Period 2	
	Before occlusion	During occlusion	Before occlusion	During occlusion
Heart rate (beats/min)				
Control	105 ± 2	$116 \pm 6*$	103 ± 4	110 ± 4
Treatment	103 ± 2	104 ± 3	112 ± 4	104 ± 6
Mean arterial pressure (mm Hg)				
Control	95 ± 10	$79 \pm 10^*$	80 ± 11	70 ± 9
Treatment	92 ± 4	88 ± 8	93 ± 7	77 ± 8
Coronary perfusion pressure (mm Hg)				
Control	70 ± 9	56 ± 9*	59 ± 10	45 ± 8*
Treatment	63 ± 4	62 ± 8	74 ± 7	53 ± 7*
Stroke volume index (ml-beats -1-m-2)				
Control	42.6 ± 4.7	$31.0 \pm 5.3^{*}$	$29.2 \pm 4.1 \dagger$	23.9 ± 4.4
Treatment	25.2 ± 3.3	22.2 ± 1.4	27.4 ± 4.5	$11.4 \pm 1.9 ^{*}$ ‡
Left ventricular stroke work index (g·m ⁻² -beats ⁻¹)				*
Control	54.7 ± 10.7	$34.8 \pm 9.9^*$	$34.6 \pm 8.7 \dagger$	24.5 ± 7.3
Treatment	29.4 ± 4.0	24.9 ± 3.4	33.7 ± 7.2	$10.2 \pm 1.8^{+}$
First time derivative of left ventricular pressure (mm Hg/min)				*.*
Control	1886 ± 165	1647 ± 214	1831 ± 201	1664 ± 286
Treatment	1688 ± 219	1481 ± 199	1725 ± 170	$1350 \pm 212^*$
Vascular resistances				
Systemic (dynes-sec-cm ⁻⁵)				
Control	2584 ± 289	2776 ± 352	3107 ± 247	3359 ± 392
Treatment	4906 ± 830	4679 ± 650	4654 ± 1044	9141 ± 1553*
Pulmonary (dynes-sec-cm ⁻⁵)				
Control	307 ± 39	$561 \pm 57^*$	$453 \pm 44 \dagger$	$612 \pm 44*$
Treatment	654 ± 89	852 ± 100	580 ± 94	1691
				± 175*‡8

For the treatment group, esmolol treatment data are given under period 1, even though esmolol treatment was actually randomly assigned to either period 1 or 2 for each subject. The control group received no treatment during either period. The following symbols apply to all tables in this article, but each symbol does not necessarily appear in each table. $^*P < 0.05$ compared with before occlusion in the same period in the same group.

sion data from background and Compton crossover on-line. Regional myocardial blood flow (RMBF) was calculated from emission data (10). For each heart, En and Ep RMBF were calculated for both normal and ischemic myocardial regions by weighted averaging of the RMBF data from each tissue sample. The En Ep ratio was calculated for both normal and ischemic myocardium for each dog by using these weighted mean data.

Data from each dog were collated to allow grouped comparisons. Analysis of variance by multifactorial repeated measure design (ANOVA PC) with post hoc testing by either the Duncan test or paired t-test with Bonferroni correction was used to determine significant variability within groups. The control group was used to test the effect of time alone on the data (i.e., difference between periods 1 and 2 without any treatment). The treatment group, in which esmolol treatment was randomly allocated to only one observation period, was used to test the effect of esmolol; therefore, treatment group data are always presented as period 1 data (Tables 1 to 5), even though the actual assignment of esmolol was randomized to either period 1 or 2, and data from control and treatment groups were not statistically compared. Results are expressed as means ± SEM. A probability of chance occurrence of <5% (P < 0.05) was considered significant. All relevant institutional policies regarding the care of experimental animals were followed, and appropriate approval was obtained for this study.

Results

Six of the 23 dogs studied under this protocol were excluded from the results: 1 because of refractory hypoxemia, 1 because of severe electrolyte abnormal-

 $[\]pm P < 0.05$ compared with before occlusion in period 1 in the same group

 $[\]pm P < 0.05$ compared with during occlusion in period 1 in the same group.

 $[\]S P < 0.05$ compared with the change in period 1 in the same group

<u>Table 2</u>. Metabolic Effects of Left Anterior Descending Coronary Artery Occlusion in the Nonischemic Area (CFXv) With and Without Treatment With Esmolol

	Peri	od 1	Period 2	
	Before occlusion	During occlusion	Before occlusion	During occlusion
Oxygen content (vol %)				
Control	5.1 ± 0.9	4.0 ± 0.6	4.1 ± 0.8	4.1 ± 0.8
Treatment	5.7 ± 0.7	4.4 ± 0.6	5.5 ± 0.5	5.1 ± 1.1
Carbon dioxide tension (mm Hg)				
Control	42 ± 2	42 ± 3	39 ± 4	$45 \pm 3*$
Treatment	37 ± 4	39 ± 4	40 ± 4	43 ± 5
pН				
Control	7.36 ± 0.02	7.35 ± 0.02	7.36 ± 0.03	7.28 ± 0.03 *‡
Treatment	7.39 ± 0.04	7.37 ± 0.04	7.39 ± 0.04	$7.35 \pm 0.04*$
Base excess (mEq/L)				
Control	-0.3 ± 0.9	-0.8 ± 0.7	-2.9 ± 1.5	$-4.0 \pm 1.3 \ddagger$
Treatment	0.0 ± 1.5	-1.0 ± 1.0	1.0 ± 1.4	-1.6 ± 1.0^{4}
Glucose (mg/100 ml)				
Control	131 ± 9	114 ± 12	111 ± 11	117 ± 13 §
Treatment	116 ± 8	101 ± 14	126 ± 8	101 ± 7
Lactate concentration (mg/100 ml)				
Control	10.7 ± 4.0	9.1 ± 2.8	6.5 ± 2.1	8.8 ± 2.6
Treatment	8.3 ± 1.5	$12.6 \pm 2.5^*$	9.3 ± 1.8	$12.9 \pm 2.9^*$
Potassium concentration (mEq/L)				
Control	3.5 ± 0.2	3.4 ± 0.2	3.6 ± 0.2	3.3 ± 0.3
Treatment	3.3 ± 0.3	3.4 ± 0.3	3.9 ± 0.7	3.5 ± 0.7
Sodium concentration (mEq/L)				
Control	152 ± 3	158 ± 7	158 ± 7	149 ± 6
Treatment	156 ± 4	167 ± 7	168 ± 12	163 ± 6

For the treatment group, esmolol treatment data are given under period 1, even though esmolol treatment was actually randomly assigned to either period 1 or 2 for each subject. The control group received no treatment during either period.

Superscripts refer to comparisons as noted in Table 1.

ities, and 4 because of failure to survive both occlusion periods. Exclusion rates were not significantly different for the two groups (3 of 11 for treatment group and 3 of 12 for control group). Ventricular fibrillation (VF), treated by electrical defibrillation, occurred during LADa occlusion or during reperfusion in 6 of 11 in the treatment group and 7 of 12 in the control group. Among the six dogs in the treatment group that had VF, four were successfully defibrillated; likewise, in the control group five of seven episodes of VF were successfully defibrillated. The peak occurrence of VF was during the early portion of the reperfusion interval between the two observation periods.

In the control group, SVI and LVSWI decreased and PVR increased before LADa occlusion during period 2 compared with period 1 (Table 1). In the control group, LADa occlusion decreased SVI, CPP, and LVSWI and increased PVR; similar changes were seen in the treatment group during LADa occlusion without esmolol (period 2) but not during esmolol treatment (period 1) (Table 1).

In the nonischemic area (i.e., CFXv blood samples) only slight metabolic changes were noted during LADa occlusion. Principally, lactate concentration increased in the treatment group (Table 2). This was

in marked contrast to the metabolic changes noted during LADa occlusion in the ischemic zone (i.e., LADv blood samples) (Table 3). Both Pco₂ and lactate concentration increased significantly and Po2 and pH decreased and BE became more negative during both periods in both groups. Glucose extraction (coronary arteriovenous concentration difference/arterial concertration) was not affected in the LAD region by LADa occlusion in either group (14.6 \pm 5.6% vs 10.5 ± 6.9%, period 1 vs period 2 in the treatment group and $12.9 \pm 5.8\%$ vs $11.8 \pm 9.7\%$ for corresponding values in the control group). Lactate extraction, similarly calculated, was markedly decreased during LADa occlusion (Table 4, where negative lactate extraction values indicate net production of lactate). However, during LADa occlusion, this value was less with esmolol than without it (Table 4).

Regional myocardial blood flow was significantly decreased in both groups in the LAD area during LADa occlusion. Esmolol treatment did not appear to affect the change in RMBF with LADa occlusion because the effect in the treatment group was similar during both periods (70 \pm 14 to 9 \pm 3 ml·min⁻¹ 100 g⁻¹ with esmolol and 72 \pm 6 to 6 \pm 3 ml·min⁻¹ 100 g⁻¹ without esmolol, n = 6, P > 0.05). In contrast, the

Table 3. Metabolic Effects of Left Anterior Descending Coronary Artery Occlusion in the Ischemic Area (LADv) With and Without Treatment With Esmolol

	Per	iod 1	Period 2	
	Before occlusion	During occlusion	Before occlusion	During occlusion
Oxygen content (vol %)				
Control	7.1 ± 1.3	$2.2 \pm 0.5^*$	5.0 ± 0.9	$3.1 \pm 0.7^*$
Treatment	6.1 ± 0.5	$3.8 \pm 0.8^*$	5.8 ± 0.8	$3.1 \pm 0.8^*$
Carbon dioxide tension (mm Hg)				
Control	40 ± 2	54 ± 5*	41 ± 3	$54 \pm 4*$
Treatment	37 ± 4	49 ± 4*	41 ± 4	$55 \pm 5^{*}$
pH				
Control	7.36 ± 0.02	7.22 ± 0.04 *	7.35 ± 0.02	$7.14 \pm 0.02*$ ‡
Treatment	7.40 ± 0.04	$7.27 \pm 0.04*$	7.39 ± 0.05	$7.20 \pm 0.03*$
Base excess (mEq/L)				
Control	-1.1 ± 1.0	$-5.1 \pm 1.1^*$	-1.7 ± 1.3	$-8.9 \pm 1.2^{+}$ ‡
Treatment	0.1 ± 1.5	$-3.7 \pm 1.0^{*}$	1.3 ± 1.4	$-5.6 \pm 1.4^{\circ}$
Glucose (mg/100 ml)				
Control	129 ± 13	98 ± 8*	112 ± 11	99 ± 11
Treatment	113 ± 10	110 ± 14	131 ± 12	112 ± 11
Lactate concentration (mg/100 ml)				
Control	8.5 ± 3.1	$26.2 \pm 10.0^{*}$	8.3 ± 3.1	$25.9 \pm 9.5^*$
Treatment	9.4 ± 1.9	$25.0 \pm 5.2^*$	10.0 ± 2.2	$35.7 \pm 8.8 \%$
Potassium concentration (mEq/L)				
Control	3.8 ± 0.4	4.2 ± 0.3	3.4 ± 0.2	4.1 ± 0.4
Treatment	3.4 ± 0.5	$4.1 \pm 0.3^*$	3.8 ± 0.6	4.1 ± 0.6
Sodium concentration (mEq/L)				
Control	163 ± 7	155 ± 3	158 ± 4	149 ± 8
Treatment	161 ± 8	166 ± 5	172 ± 12	170 ± 9

For the treatment group, esmolol treatment data are given under period 1, even though esmolol treatment was actually randomly assigned to either period 1 or 2 for each subject. The control group received no treatment during either period.

Superscripts refer to comparisons as noted in Table 1.

<u>Table 4.</u> Lactate Extraction During Left Anterior Descending Coronary Artery Occlusion With and Without Treatment With Esmolol

	Period 1		Period 2	
	Before occlusion	During occlusion	Before occlusion	During occlusion
Aorta to circumflex vein				
Control	1.5 ± 8.5	2.4 ± 7.1	15.5 ± 6.0	2.9 ± 12.6
Treatment	23.2 ± 8.9	-10.8 ± 30.2	31.7 ± 3.0	-0.4 ± 13.5
Left anterior descending coronary artery to vein				
Control	14.6 ± 6.6	$-108.1 \pm 37.3^{*}$	6.7 ± 7.9	$-177.3 \pm 82.5^*$
Treatment	12.0 ± 10.1	-29.4 ± 16	27.7 ± 5.4	$-107.2 \pm 34.3 \%$

For the treatment group, esmolol treatment data are given under period 1, even though esmolol treatment was actually randomly assigned to either period 1 or 2 for each subject. The control group received no treatment during either period.

Superscripts refer to comparisons as noted in Table 1.

En:Ep flow ratio in the LAD region decreased during each period without esmolol but was unaffected during LADa occlusion with esmolol (Table 5). Both O₂ delivery and O₂ consumption in the LAD area declined during LADa occlusion but the O₂ utilization ratio (O₂ consumption/O₂ delivery) was not affected. Calculated mass kinetics of lactate (myocardial extraction or production) per minute (calculated by lactate arteriovenous differences times the RMBF)

showed greater production of lactate during ischemia without esmolol than with it, whereas values from the two sequential ischemic periods in the control group did not differ (Table 5).

Discussion

The major finding of this study is that esmolol infusion, when started before and continued through

<u>Table 5</u>. Effect of Left Anterior Descending Coronary Artery Occlusion on Metabolic and Blood Flow Variables in the Ischemic Area With and Without Treatment with Esmolol

	Period 1		Per	riod 2
	Before occlusion	During occlusion	Before occlusion	During occlusion
Ratio of endocardial-to-epicardial		-		
blood flow				1
Control $(n = 6)$	0.98 ± 0.10	0.67 ± 0.10^{4}	1.10 ± 0.10	0.70 ± 0.10 *
Treatment $(n = 7)$	1.15 ± 0.08	1.04 ± 0.17	1.20 ± 0.09	0.71 ± 0.09 *‡
Oxygen delivery				
$(ml \cdot 10^{-2} \cdot min^{-1} \cdot 100^{-1})$				
Control $(n = 5)$	16.6 ± 1.6	$3.7 \pm 1.2*$	12.4 ± 2.3	2.3 ± 0.6 *
Treatment $(n = 6)$	9.5 ± 1.3	$1.3 \pm 0.5^*$	10.6 ± 1.3	1.1 ± 0.6 *
Oxygen consumption				
$(ml \cdot 10^{-2} \cdot min^{-1} \cdot 100 g^{-1})$				
Control $(n = 5)$	9.4 ± 0.6	$1.4 \pm 0.5^*$	7.8 ± 1.3	$2.3 \pm 0.4^*$
Treatment $(n = 6)$	5.2 ± 0.8	$0.7 \pm 0.4^*$	6.0 ± 1.0	$0.8 \pm 0.15^*$
Actual mass of lactate (mg				
lactate·min ⁻¹ ·100 g of				
myocardium ⁻¹)				
Control $(n = 6)$	1.04 ± 1.18	-1.73 ± 1.15	-0.56 ± 1.28	-4.71 ± 3.14
Treatment $(n = 6)$	0.80 ± 0.87	-0.54 ± 0.37	2.97 ± 1.36	-1.13 ± 1.04 *

For the treatment group, esmolcl treatment data are given under period 1, even though esmolol treatment was actually randomly assigned to either period 1 or 2 for each subject. The control group received no treatment during either period. The numbers in parentheses indicate the number of subjects used for the data analyses—the ANOVA program eliminated incomplete data sets and some RMBF data points were lost due to technical difficulties with sample processing or reference blood sampling. Actual mass of lactate was calculated from arteriovenous difference times the RMBF.

Superscripts refer to comparisons as noted in Table 1.

LADa occlusion, decreases lactate production and hemodynamic impairment caused by ischemia. Moreover, there is relative preservation of endocardial blood flow with esmolol during ischemia, despite the fact that there was not a measurable improvement of total blood flow to the ischemic tissue, nor did regional O₂ delivery improve with esmolol.

Two periods of ischemia were induced consecutively in this study, and this segmental design could have affected the comparisons of hemodynamic and metabolic data between periods. However data from the control group showed only minor hemodynamic differences between periods both before and during LADa occlusion (Tables 1 to 4). Metabolic measurements in the control group show a higher level of acidemia and more negative BE during LADa occlusion in both CFXv and LADv samples during period 2 than during period 1, which indicates some timerelated changes in those measurements in this model. Similar changes were not apparent in the treatment group because, by experimental design, the data for that group were collated by presence or absence of esmolol treatment, not by time period. Also, in the treatment group, for all parameters, the values measured before LADa occlusion were similar to those during the two LADa occlusion periods. Thus, before LADa occlusion, values were similar during both observation periods in both groups. Also, we have obtained similar results in another untreated control

group in a different study with the same animal model (6). The control group and treatment group were different sets of animals and were studied consecutively. Accordingly some differences in baseline data are to be expected, but statistical comparison of the two groups in this model is neither appropriate nor necessary.

This canine experimental model, with its abundant coronary collateral circulation, single isolated coronary artery occlusion, and normal collateral-bed supply vessels, differs from the clinical situation, in which multiple coronary lesions of varying length and degree of stenosis are often present. Deleterious effects observed in this model might be amplified clinically. Also, beneficial effects related to abundant carine collateral flow might not occur clinically, where collateral channels are less well developed.

Given the extensive collateral flow networks in carrine myocardium, it may not be reasonable to consider the LAD and CFX samples obtained during LADa occlusion as representative of totally ischemic vs totally normal myocardium, respectively. Indeed, even during esmolol treatment, lactate concentration increased in CFXv (normal area) samples. This probably indicates some "contamination" of those venous samples with blood from the ischemic area (Tables 3 and 4). However, overall, the blood gas, pH, and metabolite measurements showed marked differences between the LAD and CFX perfusion areas

during LADa occlusion, which indicated a severely ischemic state in the LAD perfusion area.

In the treatment group, the actual mass of lactate produced by the myocardium (negative value = production), which takes into consideration the arteriovenous lactate difference as well as the blood flow to the area, was greater (worse) during ischemia without esmolol. These data (Table 5) agree with data derived from the more "conventional" calculation of lactate production (Table 4) (arteriovenous difference as percentage of arterial value) (11). In contrast, in the control group, values for the actual mass of ischemic zone lactate produced during either ischemic period do not differ significantly from control data (Table 5). This is important because it differs from the results obtained when only the fractional arteriovenous lactate difference is used to indicate lactate production (Table 4). The probable reason for this difference is the influence of actual blood flow, which is ignored by conventional lactate extraction calculations. For a given mass of lactate produced, a decreased blood flow would increase the measured concentration (mg%) of lactate in venous samples. In several recent investigations, including two that were interpreted as indicating "coronary steal," the method used to calculate lactate production did not account for any changes in myocardial blood flow, even though flow (to great cardiac vein or coronary sinus) was measured (12-14). Clearly, quantitating the degree of anaerobic metabolism requires calculation of the actual mass of lactate produced, not just the arteriovenous concentration difference.

In conclusion, we have shown that esmolol infusion, at a rate of 150 μg·kg⁻¹·min⁻¹, decreased hemodynamic impairment produced by ischemia and, at the same time, despite the marked decrease in total regional blood flow, preserved the balance between endocardial and epicardial blood flow. Esmolol infusion also decreased lactate production in the ischemic area during LADa occlusion, but the balance between regional O2 consumption and O2 delivery was not affected by esmolol. Whether a higher dose might have been more effective in this model is speculative. However, higher doses of esmolol (>200 μg·kg⁻¹·min⁻¹) have increasingly negative inotropic effects (15). Because HR was controlled artificially in this study and SVI and CPP were not affected significantly during ischemia with esmolol treatment, the metabolic changes are likely to be a direct effect of the drug, rather than an effect of hemodynamic alterations. This study indicates that use of esmolol during anesthesia could ameliorate the effects of surgical stress and hemodynamic instability in patients at risk from myocardial ischemia.

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The Overstated Risk of Preoperative Hypokalemia

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HIRSCH IA, TOMLINSON DL, SLOGOFF S, KEATS AS. The overstated risk of preoperative hypokalemia. Anesth Analg 1988;67:131–6.

To examine the relation between preoperative hypokalemia and frequency of intraoperative arrhythmias, Holter monitoring was employed in 447 patients undergoing major cardiac or vascular operations, the group at greatest risk for life-threatening arrhythmias. Based on serum potassium levels measured immediately before surgery, 57% of patients were normokalemic (\geq 3.6 mEq/L), 34% hypokalemic (\leq 1.1–3.5 mEq/L), and 9% severely hypokalemic (\leq 3.0 mEq/L). No arrhythmia occurred at any time in 63% of patients and minor arrhythmias (premature atrial and

occasional premature ventricular contractions) occurred in 16%. Frequent or complex ventricular ectopy appeared before and during operation in 92 patients (21%) but was not related to preoperative potassium level or history of long-term diuretic therapy. Frequent and complex ventricular arrhythmias were more common in patients with a history of long-term digoxin therapy or congestive heart failure. Even among these patients, hypokalemia or diuretic therapy did not increase the incidence or severity of ectopy. These data fail to support the common practice of delaying operation for acute potassium replacement in patients whose preoperative serum potassium is less than normal, even in the presence of cardiovascular disease.

Key Words: IONS-potassium.

Current practice among internists, surgeons, and anesthesiologists requires that serum potassium be measured preoperatively in all patients on long-term diuretic therapy and in most other adult patients before major operations. This is based on the widely held belief that preoperative hypokalemia predisposes to potentially life-threatening arrhythmias during general anesthesia (1,2). As a consequence, patients with less than normal potassium levels receive acute potassium replacement intravenously before surgery or have their operation postponed for oral replacement therapy. Vitez et al. (3) recently noted that intraoperative arrhythmias were no more frequent in 62 generally healthy patients with chronic hypokalemia (potassium <3.5 mEq/L) than in 88 normokalemic patients undergoing similar operations. In view of the occasional mortality from acute potassium replacement and costs of deferring surgery, they recommended operations not be post-

poned on this account alone. Few patients in their study, however, had heart disease or underwent operations commonly associated with cardiac complications and few were digitalized (4). Such patients are considered at highest risk for hypokalemic arrhythmias. For more than two decades we have not postponed operations on the basis of a routine preoperative potassium value, nor have we acutely treated low values preoperatively in a patient population perceived to be at greatest risk. We therefore undertook this prospective study to determine the relation between preoperative potassium levels and intraoperative arrhythmias during general anesthesia in patients with heart disease who are taking cardiac drugs chronically, including digitalis, before undergoing operations commonly associated with cardiac complications such as arrhythmias (Table 1).

Methods

This investigation was approved by the institutional committee for human research. All 2242 adult patients scheduled for elective cardiac or major vascular operations from December 1, 1985 to May 31, 1986 were eligible for study. Based on availability of Holter monitors, up to four patients scheduled for first

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<u>Table 1</u>. Characteristics of 447 Patients Studied for Abnormal Cardiac Rhythms During General Anesthesia

	Coronary artery bypass (n = 309) (%)	Intracardiac $(n = 64)$ $(\%)$	Vascular (n = 74)
Age >60 years	49	38	72
Males	82	75	58
Diabetes	17	11	19
Hypertension	41	30	57
Congestive heart failure	7	31	8
History of arrthythmias	12	19	11
Ischemic heart disease			
Angina	98	19	27
Previous MI	60	14	30
MI <6 months ago	22	0	C
Ventricular aneurysm	5	3	C
Previous cardiac operations	16	28	28
Chronic drug therapy			
Digitalis	17	50	20
Diuretics (K+ depleting)	20	38	24
Calcium entry blockers	76	16	27
β -Blockers	53	14	41
Antiarrhythmics	7	9	8
Serum potassium			
≥3.6 mEq/L	59	62	46
3.1-3.6 mEq/L	33	28	42
≤3.0 mEq/L	8	9	12

operations in the morning were interviewed each evening for inclusion in the study. Of 520 patients interviewed (23% of all eligible), 20 were excluded because of chronic atrial fibrillation, 28 were excluded because they had taken their usual oral potassium supplementation within 24 hours of surgery, and 10 were excluded because the admitting physician treated the preoperative potassium value, which ranged from 2.8-3.6 mEq/L, with intravenous potassium. No patient was given potassium to treat arrhythmia. In the 462 remaining patients, plasma potassium had been measured from 12-36 heurs before operation. During the preoperative interview a detailed history of cardiac disease and both long-term and recent use of antianginal drugs, digoxin, diuretics (potassium-depleting), and oral potassium supplements was obtained. The preoperative rest ECG and rhythm strips were examined for arrhythmias.

On arrival in the operating suite, lead II Holter monitoring was begun on all patients and continued throughout surgery for vascular operations. All cardiac operations required cardiopulmonary bypass. In these, monitoring was discontinued just before cannulation of the atrium because this maneuver usually induced arrhythmias and was shortly followed by infusion of potassium-containing cardioplegia solution into the coronary circulation, invalidating subse-

quent observations. Before induction of anesthesia, during air breathing, a blood sample for measurement of pH, and gas tensions and serum potassium levels was obtained from an indwelling arterial catheter and analyzed on an IL 813 pH/blood gas analyzer and a NOVA 1 sodium/potassium analyzer. These analyses were repeated approximately every 15 minutes after anesthesia throughout the observation period. Based on the serum potassium value just before induction of anesthesia, patients were subsequently grouped and identified as normokalemic (\geq 3.6 mEq/L), hypokalemic (\leq 3.0 mEq/L).

Drugs administered for anesthesia included diazepam by mouth and an intramuscular narcotic with scopolamine 0.1-0.2 mg before operation; intravenous thiopental or diazepam for induction; and halothane, enflurane or isoflurane with fentanyl for maintenance. Muscle relaxation was provided by pancuronium. Mechanical ventilation was adjusted to maintain arterial pH within 0.03 unit of the preinduction level. Ringer's lactate solution containing 4 mEq/L potassium was infused throughout the operation. Packed red blood cells were administered to 15 of the 74 peripheral vascular patients and to none of the cardiac patients during the observation period. No patient received any supplemental potassium or antiarrhythmic drug during the observation period. No patient was excluded from the study because of arrhythmia.

Printed Holter monitor scans were independently examined in their entirety by two observers (IH,DT). In 25 instances of difference in interpretation, a third interpretation by a consultant was used. Fifteen patients were excluded because their scans were uninterpretable, as a result of excessive electrocautery in 12 and monitor malfunction in 3. Scans were assessed for occurrence, frequency, and complexity of atrial and ventricular arrhythmias. For tabulation, when multiple arrhythmias appeared, the most complex or threatening of them was recorded. All ventricular arrhythmias were considered more threatening than atrial. Ventricular arrhythmias were first tabulated by frequency and complexity. To facilitate data analysis, ventricular arrhythmias were classified according to a modification of that proposed by Lown and Wolf (5): Lown 0, no premature ventricular contractions (PVC); Lown 1, occasional isolated PVC; Lown 2, frequent PVC (>1/min or 30/hr); Lown 3, multifocal PVC; Lown 4, couplets to salvos of PVC. R on T phenomenon (Lown 5) was not investigated. Scans of 447 patients comprise the data base of this report. Operations performed included 309 (69%) coronary arterial bypass grafting (CABG), 64 (14%) intracardiac

(49 valve replacements, 13 valve replacements and CABG, 2 left ventricular aneurysmectomies plus CABG) and 74 (17%) major peripheral vascular operations (36 carotid endarterectomies, 24 abdominal aortic operations and 14 femoro-popliteal reconstructions). Duration of Holter monitoring in cardiac operations averaged 63 \pm 16 minutes and, in peripheral vascular operations, 183 \pm 31 minutes.

Continuous data were compared statistically by analysis of variance and unpaired t-test, frequency data by χ^2 analysis, and the relation of frequency to degrees of hypokalemia by the Wilcoxon-Mann-Whitney test. Means are reported with standard deviations.

Results

Plasma potassium values measured 12-36 hours preoperatively were significantly higher than preinduction serum values measured in the operating room before anesthesia (Table 2). At neither sampling period were the mean potassium levels significantly lower in patients being treated with diuretics. As a group, however, patients receiving diuretics had a higher frequency of severe hypokalemia immediately before induction of anesthesia (19% vs 6%, P < 0.01). Mean serum potassium values of samples drawn at intervals after induction of anesthesia did not differ significantly from preinduction values during the observation period. By the criteria described, 256 (57%) patients had serum potassium levels that were considered normokalemic, (range 3.6-5.4 mEq/L), 152 (34%) were hypokalemic, and 39 (9%) were severely hypokalemic (range 2.1–3.0 mEq/L) (Table 1, Fig. 1).

In 280 patients (63%) no arrhythmia appeared at any time during the observation period. In 75 patients (16%) minor arrhythmias appeared. These included occasional premature atrial contractions in 24, salvos of atrial premature contractions in 28, and occasional PVC (Lown 1) in 23. Frequent or threatening ventricular arrhythmias (complex PVCs) classified as Lown 2–4 appeared in 92 (21%) patients. The frequencies of these arrhythmias were not significantly related to either preinduction serum potassium levels (Fig. 1) or to long-term diuretic therapy.

Of 92 patients with complex PVCs, 35 were Lown 2 and included 13 with one to five unifocal PVCs/min, 10 with six to ten PVCs/min, 4 with more than ten PVCs/min, and 8 with more than ten PVCs/min plus bigeminy or trigeminy. Of 38 patients with Lown 3, 23 had one to five multifocal PVCs/min, 6 had six to ten multifocal PVCs/min, 1 had more than ten PVCs/min, and 8 had more than ten multifocal PVCs/min

<u>Table 2</u>. Preoperative and Preinduction Potassium Values of 447 Patients with and without Chronic Potassium-Depleting Diuretic Therapy

	No. of patients	Preoperative plasma potassium (mEq/L)	Preinduction serum potassium (mEq/L)
All patients	447	3.86 ± 0.37*	3.57 ± 0.39
With diuretics	102	$3.82 \pm 0.37^*$	3.43 ± 0.40
No diuretics	345	$3.87 \pm 0.36^*$	3.61 ± 0.38

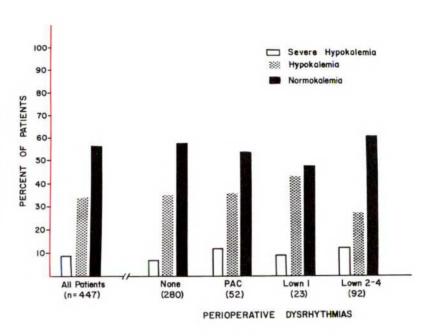
 $^{^*}P < 0.0001$ compared with corresponding preinduction potassium.

plus runs of bigeminy. Among the 19 patients with Lown 4 arrhythmias, 2 had unifocal PVCs with couplets, 8 had multifocal PVCs with couplets 1 had unifocal, and 8 had multifocal PVCs with runs of ventricular tachycardia. Runs of ventricular tachycardia never lasted more than 10 seconds and, although associated with a decrease in blood pressure, all terminated spontaneously before treatment could be initiated. As with all arrhythmias (Fig. 1), increasing severity of ventricular arrhythmia was not related to serum potassium level (Fig. 2) or to long-term diuretic therapy. Complex PVCs appeared in 22% of normokalemic patients, 16% of hypokalemic patients, and 28% of severely hypokalemic patients.

In 71 of the 92 patients with complex PVCs, the arrhythmia was present on arrival to the operating room and continued or reappeared intraoperatively in 58 of these. Complex PVCs appeared for the first time during general anesthesia in only 21 patients. Complex PVCs disappeared with anesthetic induction in 24 patients and did not recur intraoperatively in 13 of these. The appearance or disappearance of complex PVCs was not related to any specific anesthetic agent or type of operation, occurring in 19% of CABG, 22% of intracardiac, and 24% of vascular operations.

Of all patient characteristics recorded in Table 1, only patients with a history of congestive heart failure and/or ventricular aneurysm or patients with a history of chronic digoxin therapy had significantly higher incidences of complex PVCs. The relative roles of each could not be statistically distinguished (Table 3). The distribution of potassium values among the 100 patients receiving digoxin therapy were not different from the group without digoxin. In patients on digoxin, complex PVC appeared in 40% of those who were normokalemic, 27% of those who were hypokalemic, and 33% of those who were severely hypokalemic. In patients receiving long-term digoxin and diuretic therapy, the incidence of complex PVC was 40% compared with 32% of those receiving digoxin alone (P > 0.05).

Figure 1. Relative frequency of three levels of preoperative potassium values (see text) in all patients and in patients with no arrhythmias, those with atrial arrhythmias only (PAC), occasional premature ventricular beats (Lown 1), and multiple or complex ventricular ectopy (Lown 2–4). The numbers in parentheses represent the total number of patients with each arrhythmia indicated and the sum of each trio of bar graphs is 100%. Differences among groups are not statistically significant by Wilcoxon-Mann-Whitney test.



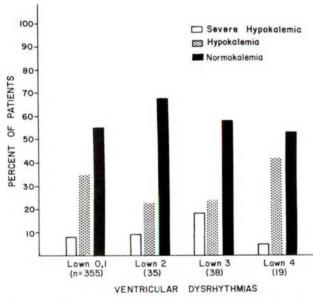


Figure 2. Relative frequency of three levels of preoperative potassium values (see text) in patients with no (Lown 0) or occasional premature ventricular beats (Lown 1), frequent unifocal premature beats (Lown 2), multifocal ventricular beats (Lown 3), or ventricular ectopy with couplets or salvos of ventricular beats (Lown 4). The numbers of parentheses represent the total number of patients with each arrhythmia indicated and the sum of each trio of bar graphs is 100%. Differences among groups are not statistically significant by Wilcoxon-Mann-Whitney test.

Premature ventricular complexes were present on the routine preoperative ECGs of 28 patients, only 1 of whom had a history of arrhythmia treated on a long-term basis with an antiarrhythmic. As expected, complex PVCs occurred in 61% of these patients during the longer Holter observation period compared with 18% of patients with normal preoperative ECGs (P < 0.001).

Discussion

The hazard of chronically low serum potassium values and their role in predisposing to ventricular ectopy are currently the subject of lively debate (6,7). Although some reports continue to confirm a relation between chronic hypokalemia and ectopy (8,9), equally compelling data fail to support a relation (10,11), fail to show that correction of low potassium values reduces ectopy (12), and fail to show an association between long-term diuretic therapy and either hypokalemia or ectopy (13,14). At issue in the debate is the high cost (6) of unnecessary potassium therapy and the potential life-threatening complications of therapy (3,6,15).

During anesthesia and operation, patients are routinely monitored for arrhythmias using electrocardiographic oscilloscopes. Depending on the sensitivity of detection and population sampled, intraoperative ventricular ectopy has been reported in 9 to 30% of all patients during all types of anesthesia and surgery (16,17,18). None of these reports addressed either the role of preoperative hypokalemia or the significance of the observed arrhythmias in terms of outcome. Despite this, the common medical practice of treating chronic hypokalemia secondary to diuretic therapy was extended to the preparation of all patients for major surgery. In the only study that examined this practice, Vitez et al. (3) failed to find a relation between preoperative hypokalemia (based on preoperative serum levels) and intraoperative ventricular ectopy in 150 patients. However, because among these 150 patients only 23% had heart disease, only 6% were on digitalis therapy, and only 29% under-

Table 3. Incidence of Ventricular Arrhythmias in Patients with and without Congestive Heart Failure (CHF), Left Ventricular Aneurysm (LVA), and Chronic Digoxin Therapy

	Preoperative characteristic				
	None	Digoxin only	LVA +/or CHF without digoxin	LVA +/or CHF with digoxin	
Patients (n)	335	51	12	49	
Incidence of complex PVC (%)†	15	33*	42*	38*	

 $^{^{*}}P < 0.05$ compared with patients without these characteristics ("None"). tLown 2.3.4.

went complex operations associated with ectopy, their recommendation to discontinue the practice of correcting preoperative hypokalemia may not be universally applicable. The population at risk in our study (Table 1) effectively overcomes these possible limitations. Heart disease was present in 93% of patients, 22% were being treated with digoxin, and 100% of operations could be characterized as complex and associated with potential cardiac complications. In this population we, too, failed to find a relation between preinduction hypokalemia and ventricular ectopy.

We have no explanation for the consistently lower potassium values obtained just before induction of anesthesia compared with values obtained 12-36 hours before operation. Serum potassium is reported to rise during hospitalization without therapy (19). Using the same blood samples we compared results of the hospital and operating room laboratories, compared serum to plasma values, and compared arterial to venous samples drawn simultaneously, and found no systematic difference to account for the lower preinduction values. Respiratory acidosis from preanesthetic drugs was extremely rare and even if present would have increased rather than decreased serum potassium levels. In any case, all our observations relating preinduction serum potassium concentration to arrhythmias apply equally to plasma potassium values measured the day before surgery.

As expected, patients taking digoxin and those with more advanced heart disease (LVA and/or CHF) had more frequent ventricular ectopy and greater complexity. Even in this group, however, the incidence and complexity were not related to either hypokalemia or to diuretic therapy. This is in accord with observations of Beller et al. (20) who found no relation between digitalis toxicity and the use of diuretics or the presence of hypokalemia. Davidson and Surawicz (21) similarly found a higher incidence of ventricular ectopy on admission ECGs of patients receiving digitalis therapy, but the incidence was independent of serum potassium level.

The present study was designed to address the single issue of whether acute potassium repletion

with or without deferral of operation was indicated for prevention of arrhythmias in surgical patients whose preoperative potassium level was less than normal. The design provides no information on the value of intraoperative potassium administration nor or the postoperative consequences of untreated hypckalemia. Within this context, this study clearly demonstrates that frequent and complex ventricular ectopy is common before and during surgery among patients with heart disease taking cardiac medicaticns including digoxin and undergoing cardiovascular operations likely to lead to cardiac complications. Arrhythmias were related to severity of heart disease and chronic digoxin therapy but were not related to przoperative potassium levels, diuretic therapy or, specifically, to potassium levels ≤3.0 mEq/L. These data fail to support continuation of the costly and pctentially hazardous practice of routine preoperative potassium repletion in the surgical patient based solely on determination of the preoperative potassium level.

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Mini-Dose Intrathecal Morphine for the Relief of Post-Cesarean Section Pain:

Safety, Efficacy, and Ventilatory Responses to Carbon Dioxide

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ABBOUD TK, DROR A, MOSAAD P, ZHU J, MANTILLA M, SWART F, GANGOLLY J, SILAO P, MAKAR A, MOORE J, DAVIS H, LEE J. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988;67:137–43.

To determine the safety, efficacy, and the ventilatory responses to carbon dioxide (CO_2) of mini-dose intrathecal morphine, 33 healthy women who underwent cesarean section with spinal anesthesia using 0.75% bupivacaine in 8.25% dextrose were studied. Patients were randomly assigned to receive, in a double-blind fashion, either morphine 0.25 mg (group I, n=11), morphine 0.1 mg (group II, n=10), or saline (group III, placebo group, n=12) in 0.5 ml volume mixed with the bupivacaine.

In both groups I and II excellent postoperative analgesia with long duration was obtained (27.7 \pm 4.0 and 18.6 \pm

0.9 hours, respectively, $X \pm \text{sem}$). All patients in group III required an analgesic (8 mg subcutaneous morphine) within 3 hours of spinal anesthesia. Seven patients in group I and four patients in group II developed mild pruritus that did not require treatment. Ventilatory responses to CO_2 showed no evidence of depression attributable to either the 0.25 or 0.1 mg of morphine, but significant depression of the CO_2 responses was observed in group III patients after administration of subcutaneous morphine. It is concluded that a dose as low as 0.1 mg of intrathecal morphine gives excellent analgesia with minimal to no side effects and that subcutaneous morphine is associated with marked depression of the ventilatory variables.

Key Words: ANALGESICS, MORPHINE—intrathecal. PAIN—postoperative. ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES, SPINAL—morphine.

Interest has been focused recently on the efficacy of epidural morphine in relieving postoperative pain after cesarean section (1–4). Nevertheless, the incidence of pruritus, nausea, vomiting, and somnolence was high and, on rare occasions, patients developed late respiratory depression (4). Intrathecal administration of morphine has been shown to produce excellent postoperative analgesia. The dose used has, however, varied markedly and was as high as 20 mg in one report (5). The present study was undertaken to evaluate the efficacy, the safety, and the ventilatory responses to CO₂ when very small doses of

morphine were given intrathecally for relief of pain after cesarean section.

Materials and Methods

We studied 33 healthy women at term who underwent cesarean delivery with spinal anesthesia. Patients were similar in weight, height, parity, and infant's gestational age and weight (Table 1). Informed consent was obtained from each patient and the study was approved by the Institutional Review Board. Complications during pregnancy or major organ disease excluded a patient from the study. For anesthesia during cesarean section, 0.75% bupivacaine in 8.25% dextrose was given intrathecally. The dose ranged from 9.75 to 11.25 mg.

Patients were randomly assigned to receive, in a double-blind fashion, either morphine 0.25 mg

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Table 1. Demographic data

	Group I $(n = 11)$	Group II^{\dagger} $(n = 10)$	Group III $(n = 12)$	
Maternal age (yr)	28.4 ± 1.70*	31.4 ± 2.05	30.0 ± 1.64	
Maternal weight (kg)	74.9 ± 2.85	71.2 ± 4.08	70.9 ± 3.45	
Maternal height (cm)	155.4 ± 2.14	154.9 ± 4.02	155.0 ± 2.47	
Parity				
Primiparous	3	1	4	
Multiparous	8	9	8	
Gestational age (weeks)	39.8 ± 0.61	38.8 ± 0.68	39.5 ± 0.52	
Infant weight (gm)	3575 ± 122	3650 ± 150	3779 ± 295	

^{*}Values are mean ± sem.

(group I, n = 11), morphine 0.1 mg (group II, n = 10), or saline (group III, n = 12) in 0.5 ml volume mixed with the bupivacaine.

The intensity of pain relief was assessed using a visual linear analog scale (6). This scale consisted of a 100-mm line on which the patient represented the degree of pain she was experiencing by placing a point somewhere between "no pain" and "the worst pain I have ever experienced." Each patient made such an assessment 3, 6, 12, 16, and 24 hours after induction of spinal anesthesia. Maternal respiratory rate, blood pressure, and heart rate were also measured at the same times.

Possible respiratory depressant effects of morphine were assessed using the ventilatory responses to progressive hypercapnia using a modified Read rebreathing technique (7) with a computer-controlled data acquisition system (8) as described later. Measurements were made in the recovery room after cesarean section ("baseline") and repeated 3, 6, 12, 16, and 24 hours later. Patients were observed for 24 hours for the appearance of adverse effects including pruritus, nausea, vomiting, and respiratory depression (i.e., a respiratory rate of <10 breaths/min).

If patients requested pain relief postoperatively, 8 mg of morphine was administered subcutaneously and ventilatory measurements were made 1.5 and 3 hours after administration of the subcutaneous morphine. Only patients in the placebo group requested pain relief in the immediate postoperative period.

Statistical analysis of data was performed using: 1) analysis of variances for comparison between groups; 2) paired *t*-test to compare data to control values within the same group; and 3) χ^2 to compare the incidence of side effects between groups using raw data. Differences were considered statistically significant when P < 0.05.

Neonates were evaluated by Apgar scores at 1 and 5 minutes by umbilical venous and arterial blood acid-base status, and by the Neurologic and Adaptive Capacity Scoring System (NACS) at 2 hours and 24

Table 2. Pain Relief of 50% or More as Measured on Visual Linear Analog Scale

	Group I $(n = 11)$	Group II $(n = 10)$	Group III $(n = 12)$
Duration (hours) (mean ± seм)	27.7 ± 4.0*	18.6 ± 0.9	$3.4 \pm 0.6^{\dagger}$

^{*}P < 0.05 compared to group II.

hours after birth, according to previously described protocol (9). Apgar scores were assigned by pediatricians unaware of the analgesic administration. The NACS examination was performed by a trained anesthesia research fellow. The NACS gives a numerical score, with a maximum of 40. Arbitrarily choosing 35–40 as the score denoting a vigorous baby (9), we determined the percentages of infants scoring 35 or higher and compared these in each group at 2 hours and 24 hours after birth. We also determined the percentage of infants having high scores on each of the individual test items.

Respiratory Measurements

Carbon dioxide response curves ($\Delta Ve/\Delta Per_{co}$, when V_E = minute ventilation (in L/min) and $P_{ET_{CO}}$ = end-tidal CO2 (in mm Hg) were measured using a portable, computer-controlled data acquisition system (8). It included an Apple II+ computer and measures VE, PET_{CO}. Each patient rebreathed exhaled CO2 through a two-way breathing valve attached to a 9-liter reservoir, initially filled with 5% CO₂ and the balance of oxygen. Exhaled CO2 concentrations were measured with a Beckman LB-2 infrared medical gas analyzer on samples taken through a catheter connected at the mouthpiece. The CO2 response curve was then determined by plotting Ve versus Perco. The CO₂ response slope was determined by linear regression of the data above an analytically determined breakpoint. We examined both the slope and the position of the slope at Pet_{CO_2} 50 ($\dot{V}e_{50}$). The data was stored on discs and could be recalled for editing, plotting, or statistical analyses. The system is portable, thus giving the investigator the flexibility of measuring patient responses in either the recovery room or the ward.

Results

Table 2 presents pain relief data using the visual linear analog scale. In both groups I and II excellent analgesia of long duration was obtained (27.7 \pm 4.0)

^{*}No Significant Differences Between Groups.

 $^{^{+}}P < 0.05$ compared to groups I and II.

PERCENTAGE CHANGE IN SLOPE OF CO2-RESPONSE

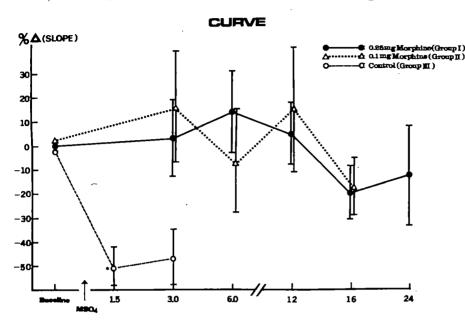


Figure 1. Percent change in CO_2 response slopes (L · min $^{-1}$. · mm Hg^{-1}) from baseline values after patients received intrathecal or subcutaneous morphine.

HOURS AFTER MORPHINE

and 18.6 ± 0.9 hours, $X \pm \text{sem}$). Three patients in group I and two patients in group II did not request additional analgesics (oral or parenteral) during their hospital stay. All patients in group III (the placebo group) required an analgesic (8 mg of subcutaneous morphine) within 3 hours of spinal anesthesia with a mean duration of analgesia of 3.4 ± 0.6 hours.

Carbon Dioxide Response Test

A complete set of CO_2 response curves were obtained in most patients. Figures 1 and 2 and Tables 3 and 4 show marked reduction in the CO_2 response slopes and VE_{50} below baseline values for group III patients after administration of subcutaneous morphine. No such reduction was observed in the other two groups. Because patients in groups I and II were given intrathecal morphine together with the local anesthetic, we were not able to obtain baseline values for their ventilatory responses to CO_2 . However, their ventilatory responses to CO_2 2.5 to 3 hours after injection of morphine were not different from those in group III, the placebo group, indicating that intrathecal morphine did not cause depression of the ventilatory variables.

Table 5 summarizes data on the incidence of side effects including pruritus, nausea, and vomiting. Urinary retention could not be assessed because

indwelling catheters in the urinary bladder were left in place for approximately 24 hours postoperatively. None of the patients had clinical evidence of respiratory depression (respiratory rate of <10 breaths/min). Sixty-four percent of patients in group I and 40% of patients in group II developed pruritus. Pruritus was frequently mild, restricted to the face and/or trunk, and often was not spontaneously reported by the patient. None of the patients required treatment for pruritus.

Effect on the Newborn

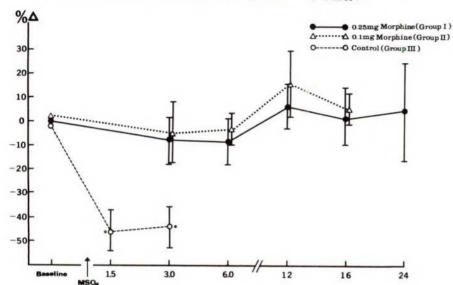
All neonates were vigorous at 5 minutes and there was no significant difference between the incidence of low 1-minute Apgar scores (6 or lower) among the three groups (Table 6).

Umbilical Arterial and Venous Blood Acid-Base Status

Umbilical artery and vein acid-base data were within normal limits in all groups and did not differ significantly with one unimportant exception of base excess, which was slightly lower in group I patients (Table 7).

PERCENTAGE CHANGE IN RESPIRATORY MINUTE

VOLUME AT P.CO2 50 TORR (VE50)



<u>Figure 2</u>. Percent change in $\dot{V}_{E_{50}}$ at Paco₂ 50 torr from control values after patients received intrathecal or subcutaneous morphine.

HOURS AFTER MORPHINE

<u>Table 3</u>. Slopes of Ventilatory Responses to CO₂ After Intrathecal or Subcutaneous Morphine (L · min⁻¹ · mm Hg⁻¹)

Time	Group I	Group II	Group I
Baseline	1.45 ± 0.13*	1.36 ± 0.23	1.58 ± 0.26
	(n = 11)	(n = 9)	(n = 12)
Hours after morphine			
1.5			$0.72 \pm 0.15^{\dagger}$
3	1.52 ± 0.36	1.57 ± 0.22	0.9 ± 0.16
	(n = 10)	(n = 9)	(n = 7)
6	1.70 ± 0.30	1.24 ± 0.19	
	(n = 10)	(n = 8)	
12	1.50 ± 0.26	1.58 ± 0.21	
	(n = 9)	(n = 8)	
16	1.13 ± 0.17	1.09 ± 0.09	
	(n = 10)	(n = 5)	
24	1.13 ± 0.23		
	(n = 6)		

^{*}Values are mean ± sem.

Neurologic and Adaptive Capacity Scores

The NACS scores of the three groups of neonates are presented in Table 8. There were no significant differences in test scores for any test item on the NACS among the three groups with the exception of the percentage of neonates who scored well on all items, which was significantly lower in group III than in group II neonates at 2 hours of age.

<u>Table 4</u>. Minute Volume (L/min) at a Paco₂ 50 Torr After Intrathecal or Subcutaneous Morphine

Time	Group I	Group II	Group III	
Baseline	22.3 ± 2.48*	24.0 ± 2.88	31.2 ± 3.97	
	(n = 11)	(n = 9)	(n = 12)	
Hours after morphine				
1.5			$14.4 \pm 2.15^{\circ}$	
			(n = 8)	
3	21.5 ± 5.26	28.0 ± 0.33	$16.6 \pm 2.54^{\circ}$	
	(n = 10)	(n = 9)	(n = 7)	
6	20.1 ± 3.57	22.9 ± 2.63		
	(n = 10)	(n = 8)		
12	24.0 ± 3.85	27.9 ± 3.19		
	(n = 9)	(n = 8)		
16	20.3 ± 1.45	24.9 ± 3.84		
	(n = 10)	(n = 5)		
24	19.8 ± 2.12			
	(n = 6)			

^{*}Values are mean ± 5EM.

Discussion

Since Wang reported the administration of intrathecal morphine for pain relief in 1979 (10), there have been several applications of this technique for relief of both chronic (11) and acute pain (5,12–15) as well as for pain associated with labor (16–18). Intrathecal morphine has been employed for postoperative analgesia in a wide range of doses, from 0.5 mg in patients after inguinal herniorrhaphy (12) to 20

 $^{^{\}dagger}$ Significantly different from baseline value (P < 0.05)

^{*}Significantly different from baseline value (P < 0.05)

<u>Table 5</u>. Percentage of Patients with Side Effects After Intrathecal or Subcutaneous Morphine

		*	
	Group I (n = 11)	Group II $(n = 10)$	Group III $(n = 12)$
Side Effects			
Pruritus	64	40	0*
Nausea	0	10	0
Vomiting	27	0	0

^{*}P < 0.05 compared with groups I and II.

Table 6. Neonates with Low Apgar Scores

	Group I (<i>n</i> = 11)	Group II (n = 10)	Group III $(n = 12)$
1 min	1	1	2
5 min	0	0	0

No Significant Differences Between Groups by χ^2 test

mg after laparotomy or thoracotomy (5). Though the literature is replete with descriptions of epidural narcotics for relief of pain after cesarean section (1–4,19–21), to the best of our knowledge no one has written about the use of the intrathecal route for this purpose. Excellent analgesia has been reported with intrathecal morphine, but several cases have been associated with life threatening respiratory depression. The safest course, therefore, would seem to be to give the minimum effective dose hoping to minimize the possibility of respiratory depression.

In our study we showed that excellent analgesia of long duration can be achieved with intrathecal doses of 0.25 mg or less. That 23% of patients required no further parenteral or oral analgesics speaks for the quality of pain relief. Morphine 0.25 mg provided a mean duration of analgesia of approximately 28 hours. Samii et al. (5) reported the same duration when using 20 mg of morphine intrathecally. Comparing the duration of analgesia after 0.25 mg of intrathecal morphine with that observed after the epidural injection of 5 mg of morphine for post-cesarean section pain relief (21) shows the duration of analgesia to be significantly longer with the intrathecal route.

Delayed respiratory depression is the most feared side effect of intraspinal narcotics (22–26). The rostral spread of morphine in the subarachnoid space to the cisterns and then to the pons is thought to be responsible for the diminished respiratory drive (27). Clinical reports of delayed respiratory depression seemed to be associated with the intrathecal injection of morphine in doses >1.0 mg (28), which is now the average dose.

Table 7. Acid-Base and Blood Gas Data

	Group I Group II $(n = 10)$ $(n = 9)$		Group III $(n = 7)$
Umbilical Vein			
pН	7.32 ± 0.01	7.32 ± 0.01	7.34 ± 0.01
Po ₂ (torr)	27.0 ± 1.7	23.2 ± 1.3	27.2 ± 2.1
Pco ₂ (torr)	45.8 ± 1.3	47.0 ± 1.8	47.3 ± 2.3
Base excess (mEq/L)	$-2.1 \pm 0.3*$	-1.3 ± 0.8	0.0 ± 0.76
Umbilical artery			
pН	7.28 ± 0.01	7.27 ± 0.02	7.26 ± 0.02
Po ₂ (torr)	18.7 ± 3.4	14.9 ± 1.7	14.7 ± 1.7
Pco ₂ (torr)	52.2 ± 2.6	52.5 ± 2.9	51.7 ± 5.5
Base excess (mEq/L)	$-1.4 \pm 5.6^{\dagger}$	-1.9 ± 1.1	-2.7 ± 1.8

^{*}P < 0.05 compared with groups II and III.

In our study none of the patients given intrathecal morphine had clinical evidence of respiratory depression. In addition, ventilatory responses to CO₂ did not show evidence of respiratory depression attributable to the intrathecal morphine, though significant respiratory depression was observed after subcutaneous morphine as well as after 5 mg epidural morphine (21). These results indicate that patients receiving traditional parenteral or epidural narcotics should be monitored carefully for signs of respiratory depression and that respiratory depression is less likely to occur when small doses of intrathecal morphine are given.

Pruritus has been reported in incidences of 2% (29) to 94% (18) after administration of intrathecal morphine. However, there appears to be a difference in the intensity of pruritus. Indeed, most of our patients were considered to have pruritus because they were observed rubbing their skin and they admitted to some pruritus on careful questioning, but none of them required any treatment.

Finally, newborns delivered of mothers given intrathecal morphine had high Apgar scores and NACS, and normal blood gas and acid-base status. The dose of morphine given is very small and would be expected to have insignificant effect on the neorate. We conclude that intrathecal administration of small doses of morphine provides excellent analgesia after cesarean section with minor side effects and with no depressant effects on ventilatory responses to CO₂. It is very likely that such low dose intrathecal morphine would also work in other operations.

We thank Drs. Phillip Bromage, Duane Sherril, and George Swanson for expert assistance with the measurement of the ventilatory responses to carbon dioxide.

 $^{^{\}dagger}P < 0.05$ compared to group III.

Table 8. The Neurologic and Adaptive Capacity Score after Intrathecal Morphine or Placebo

		2 Hours			24 Hours	
	Group I (n = 11)	Group II $(n = 9)$	Group III (n = 7)	Group 1 (n = 11)	Group II $(n = 9)$	Group III $(n = 7)$
Adaptive Capacity						
Sound	64	89	100	64	89	71
Habituation to sound	55	89	57	100	89	86
Light	82	100	86	55	67	86
Habituation to light	55	78	57	82	78	100
Consolability	100	89	100	100	100	86
Passive tone						
Scarf sign	100	100	100	100	100	100
Elbow recoil	73	100	100	100	100	100
Lower limb recoil	100	78	71	91	100	100
Popliteal angle	91	78	71	82	78	86
Active tone						
Neck flexors	27	44	14	36	56	71
Neck extensors	27	44	14	45	67	57
Palmar traction	82	78	57	73	56	71
Supporting reaction	82	67	57	73	56	71
Primary reflexes						
Palmar grasp	82	100	71	91	100	86
Automatic walking	18	18	11	29	44	14
Sucking	91	78	100	100	100	100
Moro response	100	100	86	100	100	100
General assessment						
Alertness	100	100	71	91	100	100
Crying	82	100	86	91	100	100
Motor activity	91	100	100	100	100	100
% of good scores on all test items	74	81*	71	80	84	84

^{*}P < 0.05 compared with group III

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A.



The Effect of Incremental Positive End-Expiratory Pressure on Right Ventricular Hemodynamics and Ejection Fraction

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BIONDI JW, SCHULMAN DS, SOUFER R, MATTHAY RA, HINES RL, KAY HR, BARASH PG. The effect of incremental positive end-expiratory pressure on right ventricular hemodynamics and ejection fraction. Anesth Analg 1988;67:144–51.

The effects of incremental positive end-expiratory pressure (PEEP) on right ventricular (RV) function were evaluated in 36 (n=36) ventilated patients. Positive end-expiratory pressure was increased from 0 (baseline) to 20 cm H_2O in 5-cm H_2O increments and RV hemodynamics and thermally derived right ventricular ejection fraction (RVEF), right ventricular end-diastolic volume index (RVEDVI), and right ventricular end-systolic volume index (RVESVI) were computed. Right ventricular contractility was determined from the analysis of RV systolic pressure-volume relations. Right ventricular ejection fraction declined from $42\pm8\%$ at baseline to $30\pm9\%$ at 20 cm H_2O PEEP.

Right ventricular end-diastolic volume index declined between 0 and 5 cm H_2O PEEP (103 \pm 42 to 92 \pm 34 $ml\cdot m^{-2}$) and then increased to 113 \pm 40 at 20 cm H_2O PEEP. Right ventricular end-systolic volume index increased from 60 \pm 31 $ml\cdot m^{-2}$ at baseline to 79 \pm 34 $ml\cdot m^{-2}$ at 20 cm H_2O PEEP. The slope (E) of the relation of RV peak systolic pressure to RV end-systolic volume index decreased from 0.26 mm $Hg\cdot m^2\cdot ml^{-1}$ between PEEP of 0–15 cm H_2O to 0.05 mm $Hg\cdot m^2\cdot ml^{-1}$ at PEEP > 15 cm H_2O . It is concluded that low levels of PEEP have a predominant preload reducing effect on the RV. Above 15 cm H_2O PEEP, RV volumes increase and E decreases, consistent with increased RV afterload and a decline in RV contractility.

Key Words: HEART, MYOCARDIAL FUNCTION—right ventricle. VENTILATION—positive end-expiratory pressure.

Positive end-expiratory pressure (PEEP) may impair right ventricular function by increasing right ventricular afterload. Although the salutary effects of PEEP on functional lung volume and pulmonary blood oxygen uptake have been well defined (1–5), the role of the right ventricle in PEEP-related decreases in cardiac output has not been extensively investigated.

As early as 1948, Cournand et al. (6) demonstrated that continuous positive pressure ventilation (CPPV) decreased cardiac output in humans. Since that report, numerous investigators (7–10) have shown that

there is a dynamic relation between mechanical lung expansion and right and left ventricular function. Such alterations in cardiocirculatory function have generally been ascribed to a peripheral translocation of central blood volume and decreased biventricular preload (11).

Data (12–14) suggest that this heart–lung interaction is complex. Because PEEP exerts a Starling resistor effect on the pulmonary microcirculation (15,16) and increases pleural pressure (17), the right ventricle (RV) is exposed to reduced preload and increased afterload. Right ventricular volume, which is dependent on both preload and afterload, has been reported to increase (18), decrease (19), or remain unchanged (20) during PEEP. Further, RV ejection is afterload dependent (21) and might be decreased during PEEP. This could decrease the filling of the left ventricle (LV) during diastole.

Recent studies have demonstrated a number of possible mechanisms for RV-related decreases in car-

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diac output during conditions of increased RV afterload. In addition to the aforementioned changes in loading conditions, these include leftward septal displacement (22), systolic (23,24) and diastolic (25) ventricular interdependence, and altered cardiac geometry (26,27). Much of this work, however, has been limited by major interstudy differences and hindered by a lack of reliable, reproducible serial volume and ejection phase determinations for the right ventricle because of its complex structural and functional relations.

The purpose of this study was to test the hypothesis that PEEP, by increasing RV outflow resistance, might significantly alter the characteristics of right ventricular ejection. Using thermodilution methods, we sequentially analyzed the relation between PEEP and beat-to-beat right ventricular ejection fraction and right ventricular end-systolic and end-diastolic volume indices. RV contractility was extrapolated from RV end-systolic pressure–volume points.

Methods

Patients

In accordance with the investigational guidelines of the Yale University School of Medicine and following the execution of informed consent, 36 ventilated patients demonstrating a PEEP requirement were evaluated. There were 15 women and 21 men. The mean age was 51 years (range 22 to 96).

Eighteen patients (No. 1-18) were studied within 48 hours of anesthesia and surgery. All patients were at a stable hemodynamic state, exhibiting <10% variation in blood pressure, heart rate, and right heart pressures over a 1-hour period of observation. In all cases, PEEP was instituted for reasons of postoperative hypoxemia related to increased intrapulmonary shunt ($Pao_2 < 60 \text{ mm Hg on an } Fi_{o_2} >$ 0.5). All patients were sedated with standard dosages of morphine sulfate (0.1 mg/kg IV) and diazepam (0.1 mg/kg IV). Anesthetic techniques were similar in all patients, consisting of induction with intravenous thiopental sodium (4-6 mg/kg) and tracheal intubation with a cuffed endotracheal tube (7.5-8.5 mm ID) after paralysis with succinylcholine (1.0 mg/kg). Anesthesia was maintained with enflurane or isoflurane at mean alveolar concentrations of 1-2% or fentanyl (30–75 μ g/kg). The patients inhaled oxygen and/or mixtures of nitrous oxide: oxygen with relative flow rates of 3:2. Surgical procedures among study patients included: aortocoronary artery bypass procedures (n = 7), aortic valve replacement (n = 2), partial septectomy for idiopathic hypertrophic subaortic stenosis (n = 1), cholecystectomy with common bile duct exploration (n = 1), exploratory laparotomy (n = 1), hepatic lobectomy (n = 1), nephrectomy (n = 1), and thyroidectomy (n = 1).

An additional 18 patients (No. 19–36) were within 48 hours of the institution of mechanical ventilation and PEEP for acute respiratory failure related to the following medical conditions: aspiration pneumonia (n = 4), gram-negative pneumonia (n = 4), decompensated chronic obstructive pulmonary disease (n = 7), sepsis (n = 2), and neurogenic pulmonary edema related to subarachnoid hemorrhage (n = 1).

None of the patients had a prior history of left ventricular (LV) dysfunction or prior history of intrinsic pulmonary disease. None was receiving inotropic or chronotropic support, and all maintained sinus rhythm or sinus tachycardia.

Mechanical Ventilation

Mechanical ventilation in all patients at baseline consisted of CPPV, which was maintained with a Bear II ventilator (Bear Medical Systems, Inc., Riverside, CA) set at constant tidal volume (mean 12 ml/kg), inspired fraction of oxygen (FI_{o2}) (mean 0.50), and ventilatory rate to achieve eucapnea as PEEP was incrementally raised from 0 to 20 cm H₂O in 5-cm H₂O steps. Following each PEEP adjustment, 15 minutes were allowed for the equilibration of systemic hemodynamics and pulmonary gas exchange. The entire PEEP trial required 60 minutes. Arterial blood gas measurements at each level of PEEP reflected arterial oxygen tensions (Pao₂) in the range of 60–80 mm Hg.

Hemodynamic Measurements

Clinical monitoring in all patients included a radial arterial catheter and a modified thermodilution pulmonary artery catheter with a rapid response thermistor (28). A proximal port was located at 14 cm from the distal tip to allow continuous right ventricular pressure monitoring. Hemodynamic measurements taken at end-exhalation at 0, 5, 10, 15, and 20 cm H₂O PEEP included: heart rate (HR), mean arterial blood pressure (MAP), right atrial pressure (RAP), right ventricular end-diastolic pressure (RVEDP), right ventricular peak-systolic pressure (RVPSP), pulmonary artery mean pressure (PAMP), pulmonary artery systolic pressure (PASP), and pulmonary artery occlusion pressure (PAOP). Transmural cardiac chamber pressures were estimated by

subtracting the increment in RAP from the intracardiac chamber pressures. The change in RAP during alterations in ventricular loading conditions has been highly correlated with changes in pericardial pressure (29).

All pressures were obtained using a Bentley physiologic pressure transducer which was zero-referenced to a phleobostatic axis in the midaxillary line at the level of the left atrium, digitized, and inscribed (Electronics for Medicine, Honeywell, Inc., Pleasant-ville, NY).

Derived hemodynamic parameters were calculated from the following formulas:

Cardiac Index (CI) = CO/BSA
(L·min⁻¹·m⁻²)
Stroke Volume Index (SVI) = CI/HR
(ml·beat⁻¹m⁻²)
Pulmonary Vascular Resistance Index (PVRI) =
80(PAMP-PAOP)/CI (dynes·sec·cm⁻⁵m⁻²)
Systemic Vascular Resistance Index (SVRI) =
80(MAP-RAP)/CI (dynes·sec·cm⁻⁵·m⁻²)

Right Ventricular Ejection Fraction and Right Ventricular Thermal Volume Determination

Right ventricular ejection fraction (RVEF) was calculated from the analysis of the first order exponential decay of a thermodilution cardiac output curve, which was obtained from a rapid response (1200 ohm resistance, 50 msec sensitivity) thermistor tipped Swan-Ganz catheter (model 93A-431H-7.5F, American Edwards Laboratories, Irvine, CA) (30). This technique has been validated in dogs (28,31) and in humans using radionuclide (28,32) and echocardiographic (33) techniques. RVEDVI and RVESVI were calculated according to the following formulas:

Right Ventricular End-Diastolic Volume Index (RVEDVI) = SVI/RVEF (ml·m⁻²)
Right Ventricular End-Systolic Index (RVESVI) = RVEDVI-SVI (ml·m⁻²)

Right Ventricular Contractility

The mean RVPSP and RVESVI were plotted. These points were then analyzed by linear regression. Right ventricular contractility was determined by the slope (E) of the relation of RVPSP to RVESVI. Previous studies have established that this relationship is independent of preload, linear with changes in afterload, and sensitive to alterations in contractile state in

isolated animal hearts (34). This relation has been used to describe right ventricular contractility in humans (35). Substitution of peak for dicrotic notch pulmonary artery pressure does not alter the linearity of this relation (36).

Statistical Methods

Data are expressed as mean \pm 1 sp. Analysis of hemodynamic data was performed using one-way analysis of variance with Neuman-Keuls multiple comparison test. The slope and volume intercepts of the systolic pressure–volume relation were calculated by linear regression analysis. A *P* value of < 0.05 was considered significant.

Results

Means and standard deviations of all cardiorespiratory data at 0, 5, 10, 15, and 20 cm $\rm H_2O$ PEEP are shown in Table 1. Right ventricular and pulmonary artery pressures are reported as transmural pressures. Systemic arterial and right atrial pressures are reported as direct measurements.

There were no differences in the hemodynamic responses to PEEP between the surgical (1–18) and the medical (19–36) patients. Therefore, all 36 patients were considered as one group.

Ventricular Preload

RVEDVI initially decreased from $103 \pm 42 \text{ ml·m}^{-2}$ at baseline at $92 \pm 34 \text{ ml·m}^{-2}$ at $5 \text{ cm H}_2\text{O}$ of PEEP (P < 0.05) and increased thereafter to $113 \pm 40 \text{ ml·m}^{-2}$ at $20 \text{ cm H}_2\text{O}$ of PEEP (P < 0.05). Transmural RVEDP increased from $6 \pm 4 \text{ mm}$ Hg to $7.8 \pm 3.7 \text{ mm}$ Hg, but did not achieve statistical significance (Fig. 1). Changes in transmural right ventricular end-diastolic pressure did not correlate with changes in RVEDVI (r = 0.35, P = 0.6) over the range of 0–20 cm H₂O of PEEP. Large increases in RVEDVI were associated with insignificant changes in transmural RVEDP.

Transmural PAOP showed no significant change with incremental PEEP, (14 \pm 6 to 8 \pm 4 mm Hg, at 0 and 20 cm H₂O PEEP, respectively).

Ventricular Afterload

Pulmonary vascular resistance index (PVRI) increased with incremental PEEP from 73 \pm 62 dynes-sec·cm⁻⁵·m⁻² at PEEP 0 to 365 \pm 151 dynes-sec·cm⁻⁵·m⁻² and 20 cm H₂O, respectively (P < 0.05). Right ventricular end-systolic volume index

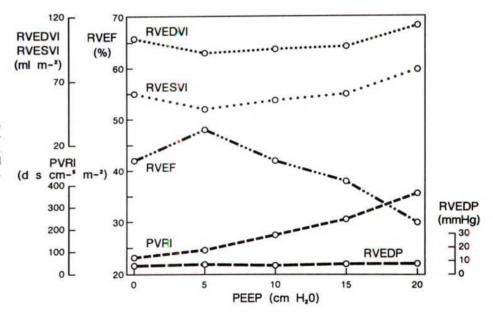
Table 1. Means and Standard Deviations of Cardiorespiratory Data at 0, 5, 15, and 20 cm H₂O of PEEP

DEED (II ())	0	5	10	15	20
PEEP (cm H ₂ 0)	U	3	10	13	20
HR (beats/min)	101 ± 15	102 ± 15	103 ± 15	105 ± 16	103 ± 16
MAP (mm Hg)	95 ± 9	95 ± 10	94 ± 10	92 ± 11	92 ± 9
RAP (mm Hg)	10.3 ± 3.2	11.3 ± 3.0	13.0 ± 2.3	14.8 ± 3.1	$16.5 \pm 3.5^*$
RVEDPtm (mm Hg)	6 ± 4	7 ± 3.8	6.3 ± 4.1	7.5 ± 4.2	7.8 ± 3.7
RVPSPtm (mm Hg)	38 ± 6	37 ± 6	38 ± 4	42 ± 5	$43 \pm 6^*$
PAMP tm (mm Hg)	18 ± 6	19 ± 4.2	21 ± 3.4	$22 \pm 4.6^*$	$24 \pm 5*$
PASP tm (mm Hg)	39 ± 7	43 ± 6	44 ± 6	46 ± 6	$48 \pm 7^*$
PAOPtm (mm Hg)	14 ± 6	13 ± 6.2	12 ± 7.9	10 ± 5.1	8 ± 3.7
CI (L·min ⁻¹ · m-2)	4.39 ± 2.2	4.50 ± 2.2	4.10 ± 1.7	3.89 ± 1.7	3.50 ± 1.6
RVEF (%)	42 ± 8	48 ± 16	42 ± 15	38 ± 11	$30 \pm 9*$
RVEDVI (ml·m ⁻²)	103 ± 42	$92 \pm 34*$	95 ± 28	97 ± 43	113 ± 40
RVESVI (ml·m ⁻²)	60 ± 31	48 ± 32	55 ± 31	60 ± 34	$79 \pm 34*$
PVRI (dynes·sec·cm ⁻⁵ ·m ⁻²)	73 ± 66	107 ± 72	175 ± 105	$247 \pm 150^*$	$365 \pm 151^*$
SVRI (dynes· sec· cm ⁻⁵ ·m ⁻²)	$1544~\pm~201$	1488 ± 254	1580 ± 310	1587 ± 347	1725 ± 326

P < 0.05.

Abbreviations: PEEP, positive end-expiratory pressure; HR, heart rate; MAP, mean arterial blood pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVPSP, right ventricular peak systolic pressure; PAMP, pulmonary artery mean pressure; PASP, pulmonary artery systolic pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; RVEF, right ventricular ejection fraction; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

Figure 1. Means (standard deviations deleted for clarity, please refer to Table 1) of transmural RVEDP, RVEF, RVEDVI, RVESVI, and PVRI plotted as a function of PEEP of 0, 5, 10, 15, and 20 cm H₂O.



(RVESVI) also increased with PEEP from 60 \pm 31 ml·m⁻² to 79 \pm 34 ml·m⁻² at PEEP 0 and 20 cm H₂O, respectively (P < 0.05). Systemic vascular resistance index (SVRI) did not change with increasing PEEP.

RV Ejection Fraction and Cardiac Index

PEEP-induced increases in PVRI were directly related to increases in RVEDVI (r = 0.78, P < 0.05) and RVESVI (r = 0.72, P < 0.05) and were inversely related to changes in RVEF (r = -0.83, P < 0.05). RVEF declined with PEEP from $42 \pm 8\%$, at baseline,

to 30 \pm 9% at 20 cm H₂O PEEP (P < 0.05). Cardiac index (CI) decreased from 4.4 to 2.2 L·min⁻¹·m⁻² at baseline to 3.5 \pm 1.6 L·m⁻¹·min⁻² at 20 cm H₂O (P < 0.05). The rate of change of CI and RVEF were compared. Cardiac index decreased at 1/2 the rate of decline of RVEF (Fig. 2). The ratio of RVEF/CI remained constant at PEEP 0–15 cm H₂O and decreased at PEEP > 15 cm H₂O.

RV Contractility

The slope of the relation between mean RVPSP and mean RVESVI, at each PEEP level, remained constant

tmTransmural pressure.

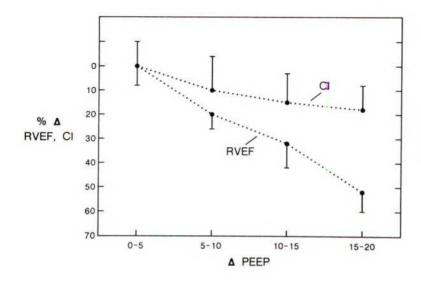
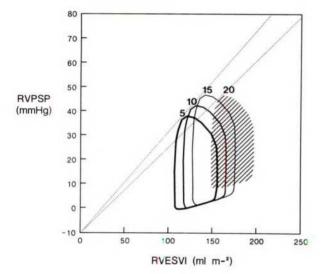


Figure 2. Percent change (% Δ) in RVEF and CI. Note that RVEF decreased at a greater rate than CI, indicating an increase in RV volume in association with decreased RV stroke output.



<u>Figure 3</u>. RVPSP—RVESVI plots indicating transmural RVPSP increasing in the linear relation (constant contractility) with increasing RVESVI during incremental PEEP up to 15 cm $\rm H_2O$ (as shown by open pressure-volume loops). At PEEP > 15 cm $\rm H_2O$, the slope of this relation decreased (as shown by the shaded pressure-volume loop), indicating a decrease in RV contractility.

at 0.26 mm $Hg \cdot m^2 \cdot ml^{-1}$ from 0–15 cm H_2O . At PEEP > 15 cm H_2O , this slope decreased to 0.05 mm $Hg \cdot m^2 \cdot ml^{-1}$ (P < 0.05) as the mean pressure–volume point fell off the line of constant contractility. This is illustrated by the integration of these data, under assumed conditions of isovolumic contraction and relaxation, into the construction of RV function loops (Fig. 3). Right ventricular function loops between 5 and 15 cm H_2O PEEP showed a linear increase in RV systolic pressure and volume consistent with an increase in RV afterload at constant contractility. The RV function loop at 20 cm H_2O PEEP was displaced downward and to the right, consistent with impaired RV function.

Discussion

Despite previous interpretations that positive endexpiratory pressure (PEEP) decreases cardiac output by decreasing biventricular preload, data from this study suggest that the decline in cardiac output during PEEP is related in part to increases in RV afterload and decreases in RV contractile state. Because PEEP alters the state of lung inflation and increases transpulmonary distending pressure, both pleural pressure and pulmonary vascular resistance may change concomitantly with incremental changes in PEEP. If alveolar distending pressure increases relative to pleural pressure, RV afterload will be increased. If pleural pressure increases relative to alveolar distending pressure, then RV preload will be reduced. The net balance of these two effects will determine the loading conditions of the RV. Because the pulmonary circulation mechanically couples RV outflow to LV inflow, large increases in RV outflow impedance limit RV ejection and thereby decrease LV diastolic filling.

Apart from a previous emphasis on the effect of PEEP on left ventricular preload, there is considerable data implicating RV and LV interdependence as a significant determinant of global cardiac output during PEEP. In open chest canine studies, Scharf et al. (37) demonstrated that PEEP increased RV septallateral dimension, causing a conformational change of the left ventricle. LV septallateral wall dimension decreased out of proportion to the LV apex-base dimension. In this preparation, RV outflow impedance induced by PEEP of 15–20 cm H₂O produced RV configurational and hemodynamic effects analogous to those seen with direct pulmonary artery occlusion. Right ventricular and LV chamber pressures increased in direct relation to RV dimensions. Right

ventricular pressure overload was associated with significant decreases in left ventricular stroke work over a wide range of left atrial pressures. These data support a distinct downward and rightward shift of the left ventricular function curve, implying impaired LV contractility on the basis of RV overload. In a closed chest model, Haynes et al. (38), using radiopaque markers, documented similar reductions in LV dimensions during PEEP, which was also assumed to be related to RV overload. In subsequent studies, Rankin et al. (39) have shown that 20 cm H2O PEEP resulted in decreased LV biplane dimensions (anteroposterior and septalposterolateral) in association with increased RV septal-free wall dimension. In particular, this work assessed the hemodynamic response of the RV to increased pulmonary arterial impedance. Within three to five beats of PEEP application, the RV dimension increased and the LV dimension decreased. Within ten beats biventricular geometry reached a new equilibrium state. Right ventricular dimension returned to baseline and LV dimension was significantly reduced. These results are consistent with a balanced RV preload and afterload effect.

In humans, a similar but more varied response to PEEP has been described. In ten normal subjects, Cassidy et al. (40) documented that 10 cm H₂O PEEP increased echocardiographically derived RV area in association with increasing transmural RAP. Likewise, in ten patients with the adult respiratory distress syndrome, Jardin et al. (41) studied the effect of PEEP on LV dimension over a range of 0–30 cm H₂O with volume loading. They confirmed the relation between PEEP-induced RV pressure overload and decreased LV compliance.

Unlike LV configuration, which lends itself to volume calculation from dimension measurements, RV volume assessment is hindered by its complex crescentic shape. The recent development of high sensitivity, low impedance thermistors for pulmonary artery catheters permits the accurate (28,30–33, 42–44) beat-to-beat calculation of RV volume. Using this thermodilution technique to calculate RV volumes and ejection fraction, the dynamic response of the RV was determined over a wide range of altered loading conditions induced by PEEP.

In our patients, a significant initial decline in RV volume was found at a low level of PEEP (0–5 cm H₂O) consistent with a decrease in RV preload. This was followed by increases in RV volume at higher levels of PEEP (15 and 20 cm H₂O), consistent with either increased RV afterload or a decline in the contractile state of the RV. Progressive increases in RV volume occurred concomitantly with decreases in

RVEF and stroke volume index (SVI). These changes were associated with modest increases in transmural RV chamber pressure. As PEEP was increased, the rate of decline in RVEF was significantly greater than the rate of decline in stroke volume index, consistent with increasing RV volume in the face of declining cardiac output.

Because RV systolic performance is load sensitive, it is uncertain whether the decline in RV function found in our patients is secondary to changes in loading conditions and/or alterations in the pumping capacity of the RV. In experimental preparations (45), stepwise increases in pulmonary artery pressure led to elevations in RV volumes, RVEDP and RV systolic pressure and to declines in stroke volume and RVEF. However, RV contractility remained preserved until pulmonary artery pressures were raised to critical levels above 60 mm Hg. At that point, RV ischemia occurred and RV failure ensued due to marked elevations in wall stress.

In preparations in which loading conditions are changing, load-independent indices of systolic function are required to determine whether the contractile state of the RV is altered. In an experimental preparation, Maughan et al. (34) described the end-systolic pressure–volume relation for the RV, which is independent of preload, linear with changes in afterload, and sensitive to the contractile state. Konstam et al. (36) expanded this relationship to studies on RV function in humans.

In this study, we have plotted the mean RVPSP–RVESVI point for all patients at each PEEP level. The linearity and positive slope of this relation between 5 and 15 cm H₂O PEEP is consistent with increasing levels of RV afterload at constant contractility. The mean pressure–volume point at 20 cm H₂O is displaced from the line of identity. Either the slope of the relation declined or the volume intercept increased. Either change would be consistent with a decline in RV contractility at high PEEP.

Recent reports by Ditchey et al. (46) in experimental preparations and Tyberg et al. (29) in cardiac surgery patients have established that changes in pericardial pressure with PEEP and volume loading, respectively, are manifested by increments in right atrial pressure. Based on these findings one can assume that the RV can accomodate large increments in ventricular volume with minimal changes in diastolic pressure. Our data, showing significant increases in RV volume and minimal increases in RVEDP with PEEP, support these conclusions.

To summarize, this paper demonstrates that PEEP has a major afterload effect on the right ventricle. This effect is manifested by increasing RV volume and

decreasing RV ejection fraction. Above a critical level of PEEP of 15 cm H₂O, RV contractility declines, presumably on the basis of increased RV wall stress.

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Ionized Hypocalcemia after Fresh Frozen Plasma Administration to Thermally Injured Children:

Effects of Infusion Rate, Duration, and Treatment with Calcium Chloride

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COTÉ CJ, DROP LJ, HOAGLIN DC, DANIELS AL, YOUNG ET. Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: effects of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 1988;67:152–60.

A number of cardiac arrests and severe hypotensive episodes have been witnessed associated with the intravenous infusion of fresh frozen plasma (FFP). To clarify the possible role of hypocalcemia, 28 thermally injured anesthetized pediatric patients with massive blood loss were studied to examine the cardiovascular responses (mean arterial pressure [MAP], heart rate, ECG) to 49 infusions of FFP. Rapid, statistically significant reductions in ionized calcium ([Ca2+]) followed each of four rates (1.0, 1.5, 2.0, and 2.5 ml·kg⁻¹·min⁻¹ for 5 minutes) of FFP infusion (P <0.0001). The slowest rate resulted in significantly less reduction in [Ca²⁺] than did the higher infusion rates (P < 0.002). In five children MAP decreased ≥20% below baseline levels, but this was not correlated with rate of FFP administration or decrease in [Ca2+]. The decreases in [Ca2+] and MAP were inversely related to age and unre

lated to anesthetic technique. Changes in the Q-oT, interval were not related to [Ca2+]. Adverse cardiovascular responses and reduced [Ca2+] were not significantly different between 5- and 10-minute FFP infusions. Fewer fluctuations in MAP occurred when calcium chloride (CaCl₂) was administered; the least fluctuation in [Ca²⁺] occurred when CaCl2 was administered during the plasma infusion. It is concluded that in thermally injured children 1-17 years old: 1) Rapid infusions of FFP produce sudden but evanescent decreases in [Ca2+]; more rapid infusions result in greater reductions in [Ca2+]. 2) There is no correlation between [Ca²⁺] and systemic hypotension. 3) Clinically important decreases in MAP occasionally accompany the rapid infusion of FFP. 4) The duration of FFP infusion does not seem to be a significant factor in causing decreases in [Ca²⁺] or in MAP. 5) Pretreatment with exogenous calcium may reduce the incidence of cardiovascular instability; smaller fluctuations in [Ca²⁺] occur if exogenous calcium is administered during the FFP infusion. 6) Changes in O-oT, are not predictive of acute changes in [Ca2+].

Key Words: BLOOD, PLASMA—fresh frozen. IONS, CALCIUM—ionized. COMPLICATIONS—burns.

The infusion of large volumes of citrated whole blood has been demonstrated to depress left ventricular function (1–3). The mechanism is citrate-induced ionized hypocalcemia, which occurs whenever citrated blood products are rapidly administered (4–7). We reviewed the charts of 17 children with thermal injuries requiring intraoperative resuscitation from

July 1973 to July 1983; eight of these events occurred in 7 patients during the rapid infusion of fresh frozen plasma (FFP). These adverse events were reversed with chest compression and intravenous drugs, including calcium. Although our retrospective review could not determine the precise circumstances of these events, it appeared that the rate of FFP administration in most cases was approximately 1.0 ml·kg⁻¹·min⁻¹ or greater. We therefore undertook a prospective study of hemodynamic parameters and changes in ionized calcium ([Ca²⁺]) during controlled, rapid infusions of FFP to children who had suffered extensive thermal injuries, in order to determine if ionized hypocalcemia as a result of rapid FFP administration might be a factor in causing cardiac

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arrest. Fresh frozen plasma was administered only to replace clotting factors lost during massive transfusion, as recommended by guidelines set forth by the National Institutes of Health (8).

Methods

Institutional approval and written informed consent were obtained. Patients between 1 and 17 years of age who had suffered thermal injuries to more than 10% body surface area and who required large amounts of FFP as part of their coagulation factor replacement during surgical excision and skin grafting procedures (blood loss >1 blood volume) were candidates for study.

The initial surgical blood loss was replaced with lactated Ringer's solution, pasteurized 5% albumin, and packed red blood cells. Only those patients who had sustained blood loss >1 estimated circulating blood volume (75 ml/kg for thermally injured patients) received FFP (8); all FFP was warmed before administration. Body temperature was maintained by controlling the operating room temperature at 27-30°C, by passing the inspired anesthetic gases through a heated humidifier, by using warming blankets and radiant warmers, and by wrapping the extremities in sterile plastic bags. Controlled ventilation, measured end-expired carbon dioxide values (Hewlett-Packard capnograph model 47210A), and arterial blood gas analysis ensured stable acid-base balance. The anesthetic prescription was selected by the anesthetizing team as deemed appropriate for each patient; the age of patients studied was not controlled because patients entered the study in order of hospital admission.

Three studies, conducted from 1983 to 1985, examined cardiovascular responses (heart rate, ECG, mean arterial pressure [MAP]) and change in [Ca²⁺] for: 1) four rates of FFP infusion administered over 5 minutes, 2) treatment with calcium chloride before and during FFP infusion, and 3) two rates of FFP infusions administered over 10 minutes.

Study One

Twenty-four thermally injured children under general anesthesia for surgical excision and grafting of their wounds received FFP through a peripheral intravenous catheter. Initially, patients were randomly assigned to either of two rates: 1.0 and 1.5 ml·kg⁻¹·min⁻¹ for 5 minutes. Once these rates of infusion were found not to cause important hemody-

namic changes, the Subcommittee on Human Studies allowed the examination of two higher rates of FFP infusion (2.0 and 2.5 ml $\,\mathrm{kg}^{-1}\,\mathrm{min}^{-1}$ for 5 minutes).

Each infusion was controlled with a four-barrel infusion pump (Harvard model 2215, Harvard Instruments, Inc., South Natick, MA); FFP was administered with one to four 140-ml syringes and a network of four-way stopcocks and extension tubing. The duration of infusion and the drawing of blood specimens were timed with a stopwatch. Arterial blood pressure was monitored via an indwelling arterial cannula connected to pressure transducers calibrated over the appropriate range and recorded on a stripchart. Arterial blood gases were measured by standard electrodes, and values were corrected for temperature as indicated. Body temperature was determined by a temperature probe inserted into the distal two-thirds of the esophagus or into the nasopharynx. Lead II of the ECG was recorded. Ionized calcium in heparinized blood samples was measured by a selective calcium electrode (Nova Biomedical, Waltham, MA). All blood specimens were of equal volume and heparinized with equivalent amounts of liquid heparin (1:1,000) which occupied the dead space of 3-ml syringes; the amount of added heparin and blood was fixed to avoid sampling artifact (9). Hemodynamic data and [Ca²⁺] were recorded immediately before plasma infusion and at 1, 2, 3, 4, 5, 6, and 10 minutes from the beginning of the infusion.

Study Two

These 14 children also participated in Study One, but in this study calcium chloride (CaCl₂) 5.0 mg/kg was administered via a central venous catheter. In five children the plasma infusion rate was 1.0 ml·kg⁻¹·min⁻¹, and in five others it was 1.5 ml·kg⁻¹·min⁻¹ for 5 minutes. These 10 children received the CaCl₂ 1 minute before the 5-minute plasma infusion. Data were obtained as in Study One; additional blood samples were collected for [Ca²⁺] determination 1 minute after CaCl₂ administration. Four other children received CaCl₂ 5.0 mg/kg during the FFP infusion, immediately after the second minute.

Study Three

The protocol for Study Three was identical to that for Study One except that the duration of the FFP infusions was 10 minutes, and the hemodynamic vari-

Table 1. Demographic Data* of Children Who Received 5-Minute Infusions of Fresh Frozen Plasma

Rate FFP (ml-kg ⁻¹ -min ⁻¹)	N	Age (yr)	Weight (kg)	Surface area burned (%)	Days after thermal injury	рН	Pao ₂ (mm Hg)	Paco ₂ (mm Hg)	Temperature (°C)
1.0	7	9.3 ± 4.9	35.9 ± 17.3	59.3 ± 30.3	9.4 ± 2.3	7.39 ± 0.04	128.4 ± 18.2	37.3 ± 4.6	36.3 ± 1.0
1.5	8	4.9 ± 4.3	19.3 ± 10.1	50.0 ± 19.7	14.4 ± 13.4	7.39 ± 0.03	127.6 ± 26.2	35.8 ± 5.2	35.8 ± 0.7
2.0	6	8.2 ± 4.3	28.7 ± 15.4	47.3 ± 26.5	25.5 ± 35.1	7.42 ± 0.06	154.3 ± 30.7	34.8 ± 2.5	36.0 ± 0.3
2.5	6	4.7 ± 1.6	21.0 ± 7.7	54.7 ± 24.8	30.0 ± 52.0	7.39 ± 0.04	140.2 ± 11.4	37.3 ± 4.6	36.0 ± 0.6

*Mean ± SD.

ables and [Ca²⁺] were measured at 2-minute intervals. Four thermally injured patients received FFP at two infusion rates (1.0 and 2.0 ml·kg⁻¹·min⁻¹) during the same surgical procedure. Patients were randomized as to which dose of plasma was administered first, so that each patient acted as his own control.

Data analysis. Ionized calcium values were determined in duplicate. All ECGs recorded in patients of Studies One and Three were interpreted by an observer who was unaware of patient data. The [Ca²⁺] and hemodynamic data were analyzed by analysis of variance with allowance for repeated measures and by analysis of covariance. Significance of planned comparisons was judged according to Bonferroni t-tests, using a (simultaneous) significance level of 0.05; i.e., 0.05 was divided by the number of comparisons to obtain the significance level that an individual P-value must satisfy to achieve statistical significance (10,11). For Study One, the analysis of the data involved 16 comparisons: 5 minutes versus baseline within each of the four rates, pairwise differences in the change from baseline to 5 minutes for the six pairs of rates, and pairwise differences at baseline for the six pairs of rates. Thus, with 16 comparisons each would have to have a P-value < 0.05/16, or 0.003125 to be judged significant at the simultaneous 0.05 level. The correlation coefficient summarized the relationship, in thermally injured children, between age and the change in [Ca2+] and MAP from baseline to 5 minutes. Analyses for Study Two used the data on [Ca²⁺] and MAP from the ten children who received CaCl2 before the FFP infusion. These analyses considered three comparisons: the difference in change from baseline to 5 minutes between pretreatment and nonpretreatment at each of the two rates and the differences in change from baseline to 5 minutes between the rates in the pretreated condition. In addition, the analysis of [Ca²⁺] compared 5 minutes versus baseline within each of the four combinations of rate and pretreatment (a total of seven comparisons). For Study Three the analysis of [Ca2+] and each hemodynamic variable tested four comparisons: the change from baseline to 10 minutes at each of the two rates, the difference in these changes between the rates, and the difference between the two rates at baseline.

Results

Twenty-eight patients received a total of 49 FFP infusions; a rapid fall in [Ca²⁺] occurred 1 minute after the start of the plasma infusion in all patients. In those patients who did not receive exogenous calcium therapy, [Ca²⁺] returned close to baseline within 5 minutes after termination of the FFP infusion.

Study One

Twenty-four patients were studied on 27 occasions; 1 child was studied at two rates of infusion and another at three rates of infusion. The anesthetic drugs included nitrous oxide, intravenous morphine, and nondepolarizing muscle relaxant in 8 (balanced anesthesia), balanced anesthesia with 0.25–0.5% inspired halothane in 13, balanced anesthesia and 1.0% inspired halothane in 1, and balanced anesthesia with 0.25–0.5% inspired enflurane in 5. The demographic data and baseline variables are presented in Table 1; there were no significant differences among the subsets of patients. Table 2 summarizes the observed responses at baseline and 5 minutes.

A significant decrease in $[Ca^{2+}]$ occurred for all doses of FFP (P < 0.0001) (Fig. 1). The decrease in $[Ca^{2+}]$ was significantly greater at the rates of 1.5, 2.0, and 2.5 ml·kg⁻¹·min⁻¹ than at 1.0 ml·kg⁻¹·min⁻¹ ($P \le 0.002$); the decrease in $[Ca^{2+}]$ for the three highest rates of FFP infusion did not differ ($P \ge 0.38$). For children age 10 or younger, the decrease in $[Ca^{2+}]$ showed a weak inverse relation with age (r = -0.42, P < 0.05). Despite the decrease in $[Ca^{2+}]$, there was, on average, no statistically significant decrease in MAP at any plasma infusion rate. Individual changes in MAP varied from a decrease of 26% to an increase of 25%. Clinically important decreases in MAP

Table 2. Hemodynamic Data* of Children Who Received 5-Minute Infusions of Fresh Frozen Plasma

			rial pressure n Hg)	[Ca ²⁺] (mM/L)	Q-oT	(sec)	Heart rate	(beats/min)
Rate FFP (ml·kg ⁻¹ ·min ⁻¹)	N	Baseline	End 5-min infusion	Baseline	End 5-min infusion	Baseline	End 5-min infusion	Baseline	End 5-min infusion
1.0	7	76.4 ± 4.4	72.0 ± 5.1	1.17 ± 0.02	0.98 ± 0.04†	0.171 ± 0.016	0.174 ± 0.023	123.4 ± 4.3	124.7 ± 3.6
1.5					$0.82 \pm 0.03 + 1$			144.9 ± 8.1	149.5 ± 9.9
2.0							0.215 ± 0.037	115.5 ± 10.5	118.8 ± 8.0
2.5							0.215 ± 0.019 §		

^{*}Mean ± SEM.

 $[\]S P < 0.05$ compared to baseline.

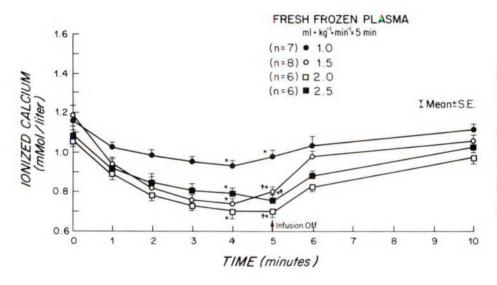


Figure 1. This figure demonstrates the decrease in $\lceil \text{Ca}^{2+} \rceil$ after 27 infusions of FFP, each of 5 minutes' duration, to thermally injured children. Note that highly significant reductions in $\lceil \text{Ca}^{2+} \rceil$ accompanied all rates of infusion (*P < 0.0001); these reductions in $\lceil \text{Ca}^{2+} \rceil$ were significantly greater for the three highest rates than for the lowest rate (†P \leq 0.0021). Ionized calcium rapidly increased within 1 minute of stopping the FFP (arrow) and approached normal values within 5 minutes.

(20–26%) occurred in five patients scattered among three different rates of FFP infusion; the age of these five patients ranged from 1.0 to 9.0 years. In those children who had a decrease in MAP, the decrease in MAP from baseline to 5 minutes was inversely related to age (r=-0.48, P=0.01). The Q-oT_c interval was prolonged only at the highest rate of plasma infusion (P=0.0028); there was no consistent relation with the decrease in [Ca²⁺] or with changes in MAP. Graphic examination of these same changes from baseline to 5 minutes under halothane anesthesia versus other anesthetic techniques showed no suggestion of a relation between anesthetic agent and the development of arterial hypotension.

Study Two

The demographic data and baseline parameters for patients in Study Two are presented in Table 3. The ten thermally injured children who received $CaCl_2\ 1$ minute before FFP infusion demonstrated greater

cardiovascular stability than when they did not receive pretreatment with exogenous calcium. The greatest decrease in MAP was 9%, and the greatest increase was 17% (increased in seven, decreased in three). When the same children received no pretreatment, the greatest decrease in MAP was 26% and the greatest increase in MAP was 10% (decreased in seven, increased in two, unchanged in one); these differences did not reach statistical significance (Table 4). Two of these patients were anesthetized with balanced anesthesia and eight with balanced anesthesia plus 0.25–0.5% inspired halothane. There were no arrhythmias or significant changes in heart rate or MAP. Both infusion rates produced a significant decrease in [Ca²⁺] from baseline to 5 minutes, both when the children were pretreated and when they were not pretreated with CaCl₂ (P < 0.001). The patients at the higher rate (1.5 ml·kg⁻¹·min⁻¹) experienced a significantly smaller decrease in [Ca²⁺] from baseline to 5 minutes when treated than when untreated (P = 0.0022); of note, however, was the sharp

[†]P < 0.001 compared to baseline.

 $[\]ddagger P < 0.002$ compared to rate 1.0.

Table 3. Demographic Data* of Children Who Were Pretreated with Calcium Chloride

Rate FFP (ml·kg ⁻¹ ·min ⁻¹)	N	Age (yr)	Weight (kg)	Surface area burned (%)	Days after thermal injury	рН	Pao ₂ (mm Hg)	Paco ₂ (mm Hg)	Temperature (°C)
1.0	5†	10.6 ± 4.9	40.3 ± 17.8	68.2 ± 31.7	8.6 ± 1.3	7.39 ± 0.04	127.0 ± 21.5	36.2 ± 1.5	36.4 ± 1.1
1.0	5‡	10.6 ± 4.9	40.2 ± 17.8	68.2 ± 31.7	12.0 ± 0.7	7.39 ± 0.04	134.6 ± 15.6	37.8 ± 4.5	35.7 ± 0.8
1.5	5t	4.1 ± 2.9	16.7 ± 4.0	54.0 ± 22.5	8.8 ± 4.1	7.39 ± 0.04	124.0 ± 14.0	34.2 ± 5.2	35.8 ± 0.6
1.5	5‡	4.1 ± 2.9	16.6 ± 4.1	54.0 ± 22.5	12.0 ± 4.7	7.43 ± 0.01	143.6 ± 41.5	35.0 ± 3.2	36.1 ± 0.8

^{*}Mean ± SEM.

Table 4. Hemodynamic Data* of Children Who Were Pretreated with Calcium Chloride

Rate FFP (ml·kg ⁻¹ ·min ⁻¹)		Mean arterial pressure (mm Hg)		[Ca ²⁺] (mM/L)		Q-oT _c (sec)		Heart rate (beats/min)	
	N	Baseline	End 5-min infusion	Baseline	End 5-min infusion	Baseline	End 5-min infusion	Baseline	End 5-min infusion
1.0	5†	74.7 ± 6.2	75.5 ± 6.6	1.18 ± 0.02	0.98 ± 0.04§	0.175 ± 0.023	0.168 ± 0.032	127.0 ± 2.5	127.6 ± 3.8
1.0	5‡	81.5 ± 7.9	84.6 ± 8.7	1.20 ± 0.02	1.06 ± 0.03 §	0.202 ± 0.011	0.196 ± 0.011	117.6 ± 3.0	120.2 ± 3.1
1.5	5†	85.5 ± 3.6	74.8 ± 5.7	1.20 ± 0.06	0.81 ± 0.048	0.170 ± 0.019	0.206 ± 0.023	139.4 ± 9.3	142.6 ± 13.6
1.5	5‡	81.3 ± 6.9	81.2 ± 5.3	1.11 ± 0.04	●.88 ± 0.05§,	0.137 ± 0.023	0.161 ± 0.025	129.8 ± 11.6	131.2 ± 13.6

^{*}Mean ± sem.

^{||}P = 0.0022 for the difference (0.156) between the change from baseline to 5 minutes when treated and the change when untreated [(pretreated, 5 minutes) - (pretreated, baseline)] - [(untreated, 5 minutes) - (untreated, baseline)].

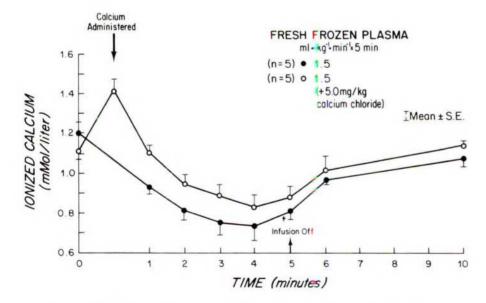


Figure 2. This figure contrasts the response of five thermally injured children when they did not receive calcium chloride before FFP infusion to that of the same five children when they did receive calcium chloride (5 mg/kg). Note the sharp rise in $[Ca^{2+}]$ produced by bolus calcium chloride administration (arrow). A significantly greater decrease in $[Ca^{2+}]$ occurred in the untreated children (tP = 0.0022).

increase in [Ca²⁺] 1 minute after calcium administration (Fig. 2).

The four children who received exogenous calcium during the FFP infusion demonstrated the least fluctuation in [Ca²⁺] (Fig. 3); MAP increased in all four patients. Two were anesthetized with balanced anesthesia and two with balanced anesthesia plus 0.25% inspired enflurane.

Study Three

Four patients received FFP infusions at 2.0 ml·kg $^{-1}$ ·min $^{-1}$ and 1.0 ml·kg $^{-1}$ ·min $^{-1}$ for 10 minutes. The demographic data (mean \pm sp) for the four patients studied twice were: age, 2.3 \pm 1.8 years; weight, 12.7 \pm 5.1 kg; percentage of burn, 53.0 \pm 24.8; days after thermal injury, 7.0 \pm 4.8; tempera-

[†]No calcium treatment.

[‡]Calcium treatment (5.0 mg/kg calcium chloride).

[†]No calcium treatment.

[‡]Calcium treatment (5.0 mg/kg calcium chloride).

 $[\]S P = 0.001$ compared to baseline.

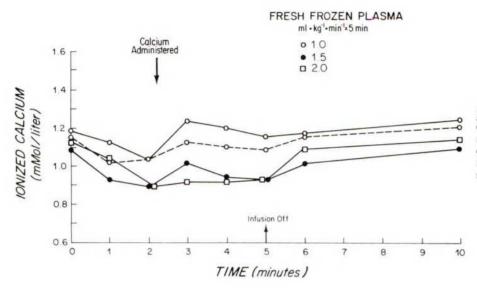


Figure 3. This figure demonstrates the change in ionized calcium in four thermally injured patients who received calcium chloride after 2 minutes of FFP infusion (arrow). Note that there were no sharp increases or decreases in [Ca²⁺]

<u>Table 5</u>. Hemodynamic Data* of Four Children Who Received Fresh Frozen Plasma at the Rates of 1.0 and 2.0 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 10 Minutes

Rate FFP (ml·kg ⁻¹ ·min ⁻¹)	Mean arterial pressure (mm Hg)		Central venous pressure (mm Hg)		[Ca ²⁺] (mM/L)		Q-oT _c (sec)		Heart rate (beats/min)	
	Baseline	End 10-min infusion	Baseline	End 10-min infusion	Baseline	End 10-min infusion	Baseline	End 10-min infusion	Baseline	End 10-min infusion
1.0	76.0 ± 8.1	73.8 ± 9.1	4.1 ± 1.2	7.2 ± 2.9	1.06 ± 0.08	0.83 ± 0.04†	0.205 ± 0.026	0.194 ± 0.013	143.2 ± 15.0	139.2 ± 10.8
2.0	75.0 ± 6.5	82.7 ± 6.6 ,¶	4.1 ± 1.8	13.5 ± 2.5†,‡	1.03 ± 0.09	0.79 ± 0.06†	$\begin{array}{c} 0.147\ \pm \\ 0.023\end{array}$	0.190 ± 0.019§	145.8 ± 9.1	146.8 ± 10.1

*Mean ± SEM.

 $\pm P < 0.0001$ compared to control.

 $\ddagger P = 0.0007$ compared to rate 1.0.

 $\S P = 0.0120$ compared to rate 1.0.

||P| < 0.005 compared to control.

 $\P P = 0.0097$ compared to rate 1.0.

ture, 37.2 ± 0.7 °C; pH, 7.36 ± 0.04 ; Paco₂, 37.0 ± 2.7 mm Hg; and Pao₂, 137.8 ± 34.7 mm Hg; each of these patients was anesthetized with balanced anesthesia. The cardiovascular effects and changes in [Ca²⁺] from baseline to 10 minutes are presented in Table 5. The higher infusion rate resulted in a slightly more rapid decrease in $[Ca^{2+}]$ between infusion rates (P > 0.25). There were no statistically significant or clinically important decreases in MAP (P > 0.5). The higher rate of FFP administration resulted in a significant elevation in central venous pressure (CVP, P <0.0001). In addition, the increase in CVP was significantly more rapid at the higher rate (P = 0.0007). The decrease in [Ca2+] at 6 minutes was comparable to that observed with the shorter infusions of the same rate at 5 minutes. There was no greater decrease in [Ca²⁺] at 10 minutes for the 10-minute infusions compared to the same rates of infusion of 5 minutes' duration at 5 minutes. Neither rate produced a sig-

nificant change in the Q-oT_c interval from baseline to 10 minutes.

Discussion

Numerous studies in adults and children have found an association between reduced [Ca²⁺] and elevated plasma citrate levels; citrate itself has no known hemodynamic effects (4–7,12,13). Ionized hypocalcemia as a result of chelation by citrate has been demonstrated to cause peripheral vasodilation and myocardial depression (1–3,14,15). Because FFP has the highest citrate concentration per unit volume of any blood product, and because its low viscosity allows rapid administration without interruption, ionized hypocalcemia is most likely to occur during FFP infusion. Pediatric patients, who have a small circulating blood volume, are potentially at risk for ionized hypocalcemia whenever FFP is transfused.

Clinically important decreases in MAP and [Ca²⁺] were observed in this study, but the correlation between [Ca²⁺] changes and hemodynamic responses did not reach statistical significance. We did not find a consistent systemic vascular response during or after the rapid infusion of FFP other than severe but transient ionized hypocalcemia.

The data show inconsistent degrees of arterial hypotension during rapid administration of FFP; this suggests an etiology that is more complex than ionized hypocalcemia alone to explain the previously observed episodes of cardiac arrest or severe hypotension. Possible contributing factors include liberation of vasoactive substances (e.g., prekallikrein activator or protease-released kininogen) from granulocytes and platelets, myocardial depression caused by potent anesthetic agents (added to that caused by ionized hypocalcemia), and variations in citrate metabolism or calcium homeostasis (16,17).

The decrease in [Ca²⁺] observed in the children with thermal injury receiving 1.5, 2.0, and 2.5 ml·kg⁻¹·min⁻¹ was nearly identical to unburned adults receiving 100–150 ml·kg⁻¹·min⁻¹ whole blood (4). There was no relation between acute reductions in [Ca²⁺] and prolongation of the Q-oT_c interval; in some children the Q-oT_c interval shortened despite severe ionized hypocalcemia; this is consistent with data of other investigators (18). The nearly identical decrease in [Ca²⁺] during 5- and 10-minute FFP infusions suggests a compensatory mechanism such as mobilization of calcium or very rapid metabolism of citrate. The increase in CVP could reflect either a volume-loading effect or myocardial depression; this is also consistent with studies in adults (4).

In a dog model, a deeper plane of halothane anesthesia has been demonstrated to produce greater myocardial depression and greater ionized hypocalcemia during rapid citrate infusion compared to lighter planes of halothane anesthesia (19). The postulated mechanism for potent inhalation agentmediated myocardial depression is an alteration in myocardial calcium transport (20-24). Therefore, it is not surprising that adverse cardiovascular events might occur when available [Ca2+] is suddenly reduced by citrate. Most of the children in this study, however, were anesthetized with a combination of narcotic, nitrous oxide, and muscle relaxant; in those patients receiving potent inhalation agents, only low concentrations of enflurane or halothane were administered. The anesthetic technique was not controlled because at the time of these clinical studies the possible effect of potent inhalation agents was unknown. Indeed, it was this clinical study that encouraged us to explore, in a dog model, the possible role of halothane anesthesia. In this clinical study, the children with the greatest decrease in MAP had different anesthetic techniques, and others with similar anesthetic drugs had no clinically important reductions in MAP; we did not find any relation between anesthetic agents and adverse cardiovascular response. Perhaps if deeper planes of anesthesia with potent anesthetic agents had been utilized, we would have observed greater myocardial dysfunction (24).

Low [Ca²⁺] values have been described in adults and thermally injured children as long as 35 days after the injury, and could possibly have contributed to the development of ionized hypocalcemia; all patients in this study, however, were normocalcemic before FFP administration (25).

Age-related responses may also be an important factor to consider, especially in neonates, in whom ionized hypocalcemia frequently occurs (13). It is known that total body calcium stores increase with age and muscle mass (26). Adult calcium stores are not achieved until adolescence with the onset of increased circulating levels of gonadotropins and somatomedin (27). Because adult somatomedin levels are achieved by age 10, we analyzed the data from patients under the age of 10 and found a weak (P < 0.05) inverse relation between decrease in [Ca2+] and age (27). Weight was not used as a covariate because of the mix in sex, ethnic origin, and tissue loss due to the burn injury. There was a strong inverse relation between decrease in MAP and age for all patients; this may reflect age-related differences in the ability to mobilize [Ca²⁺] rapidly during the hypocalcemic state, although this has not been studied. The size of our study population, the demographics of children with thermal injury, and the time required to achieve a large thermally injured study population of specific age groups requiring FFP infusion during surgery preclude a more rigorous examination of the effects of age.

Citrate metabolism may have a particularly important influence on the findings of this study. Factors that increase metabolic rate or hepatic blood flow may hasten the clearance of citrate. It is known that the thermally injured patient develops a hyperdynamic state 3 to 5 days after acute thermal injury; it is possible that increases in citrate metabolism may result purely from increased hepatic blood flow (28,29). Conversely, because citrate is primarily metabolized by the liver, any depression of hepatic blood flow may decrease citrate metabolism (30). The thermally injured patient's metabolic rate is increased by approximately 40%, and glucose and lactate turnover is increased four- to eightfold (28,29). Because citrate feeds directly into the tricarboxylic acid cycle,

it is possible that citrate is metabolized more rapidly in the thermally injured patient.

Significant renal citrate metabolism has also been demonstrated in dogs; an increase in glomerular filtration rate and renal blood flow, the normal response to thermal injury, could also partially explain the apparently rapid clearance of citrate in children with thermal injury, although this mechanism has not been studied in humans (31,32). In this study the effects of hypothermia and hypovolemia were minimal because all patients studied were within an acceptable temperature range and all were normovolemic as judged by the usual indexes (i.e., central venous pressure, contour of the arterial wave form, heart rate, and urine output (33,34).

In summary, our study suggests that children with acute thermal injuries tolerate massive citrate loads relatively well, which is the reverse of our original hypothesis.

The administration of exogenous calcium appeared to blunt adverse cardiovascular events that occasionally accompany the rapid infusion of FFP. Although the degree of ionized hypocalcemia did not clearly correlate with changes in MAP, we think that concurrent calcium replacement therapy is probably indicated during rapid FFP infusion to avoid possibly dangerous fluctuations in [Ca²⁺].

Finally, we wish to emphasize that FFP was administered only when clinically indicated to replenish clotting factors lost during massive blood loss; FFP should not be administered purely for volume replacement.

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Comparison of Effects of Atracurium and Vecuronium in Cardiac Surgical Patients

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GALLO JA, CORK RC, PUCHI P. Comparison of effects of atracurium and vecuronium in cardiac surgery patients. Anesth Analg 1988; 67:161–5.

To compare the cardiovascular effects of intubating doses of atracurium besylate and vecuronium bromide in cardiac surgical patients while utilizing fentanyl anesthesia, 20 patients scheduled for elective coronary artery bypass surgery were randomly assigned to two equal groups in a double-blind fashion. Two minutes after induction of anesthesia, baseline hemodynamic measurements were obtained and either atracurium 0.5 mg/kg (group 1) or vecuronium 0.12 mg/kg (group 2) was administered as an intravenous bolus. Hemodynamic measurements were then repeated 2, 5, and 10 minutes after injection. Atracurium produced a statistically significant decrease in blood pressure at 2 minutes and a statistically significant increase in cardiac output and decrease in systemic vascular resistance at 2, 5, and 10 minutes. Vecuronium produced no statistically

significant changes in any hemodynamic variable measured other than a decrease in pulmonary capillary wedge pressure 10 minutes after the drug was administered. The hemodynamic changes seen with atracurium were closely related to changes in serum histamine levels, whereas histamine level did not change after vecuronium. There were no statistically significant differences between the two groups, even though after atracurium statistically significant changes were observed while there were no statistically significant changes associated with vecuronium. It is concluded that when utilizing the above clinical dose range, use of vecuronium may be advantageous over use of atracurium when hemodynamic stability is crucial in the anesthetic management of cardiac surgical patients.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium, vecuronium. HISTAMINE—atracurium, vecuronium.

Atracurium besylate and vecuronium bromide are nondepolarizing muscle relaxants with intermediate duration of action. Both have been reported to be devoid of significant hemodynamic side effects in humans when used in clinically effective doses (1,2). However, other studies have indicated that atracurium may produce significant histamine release on injection, resulting in significant hemodynamic side effects when used both within and above the normal clinical dose range (3). The pharmacology of atracurium and vecuronium has been well summarized and compared to that of other currently available muscle relaxants (4). However, the majority of studies that have looked at the hemodynamic effects of these two agents are flawed by the fact that they have not

subjected these two muscle relaxants to a head-to-head comparison. One or the other has been studied, but few authors have investigated the full hemodynamic profile of these drugs using the same protocol. Thus, this study was undertaken to compare the hemodynamic effects and to investigate the histamine-releasing potential of each agent.

Methods

Twenty patients scheduled for elective coronary artery bypass surgery were randomly assigned to two equal groups by the flip of a coin. Informed consent was obtained from all patients involved and the study was approved by the Human Subjects Committee of our institution. All patients had documented multivessel coronary artery disease and were classified as Functional Class II or III according to the New York Heart Association Functional Class Scale. Patients with a history of a myocardial infarction within the last 6 months or with a demonstrated high-grade left main coronary artery obstruction, by coronary angio-

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Table 1. Group 1: Atracurium 0.5 mg/kg

	Baseline	2 min	5 min	10 min
HR (beats/min)	53.2 ± 2.1*	57.4 ± 3.2	54.6 ± 3.0	54.8 ± 3.5
SBP (systolic-mm Hg)	130.8 ± 5.4	$117.3 \pm 8.3 \dagger$	131.5 ± 8.5	135.9 ± 5.8
DBP (diastolic—mm Hg)	66.7 ± 2.8	$58.5 \pm 4.6 \dagger$	63.5 ± 3.2	65.5 ± 3.1
CO (liters/min)	$3.53 \pm .18$	$4.42 \pm .40 \dagger$	$4.51 \pm .43 $	$4.69 \pm .44 \dagger$
SVR (dynes-sec-cm ⁻⁵)	1776 ± 95	$1341 \pm 131 +$	$1465 \pm 139 \pm$	$1472 \pm 134 \dagger$
PCWP (mm Hg)	14.8 ± 1.2	12.5 ± 1.2	$12.0 \pm 1.3 \dagger$	$11.9 \pm 1.0 \pm$
% Change histamine from baseline	0*	$95.5 \pm 49.1 \dagger$	$146.8 \pm 68.6 \dagger$	59.6 ± 46.5

^{*}Mean \pm se; n = 10.

graphy, were excluded from the study. All patients had an ejection fraction >0.5 and a left ventricular end-diastolic pressure <15 mm Hg. Patients were randomly assigned, in a double-blind fashion, to receive either atracurium (group 1) or vecuronium (group 2). A research assistant not involved in the recording of hemodynamic data would perform the flip of the coin to determine the group to which the patient was assigned. Then, based on the weight of the patient, the appropriate dose of atracurium or vecuronium was placed in a syringe in a total volume of 5 ml. Sterile water was utilized as the dilutent when necessary. Five patients in group 1 and six patients in group 2 were receiving β -adrenergic blocking drugs in doses ranging from the equivalent of 10 mg to 40 mg of propranolol three times a day. Cardiac medications, including β -adrenergic blocking drugs, slow calcium channel blockers, and nitrates were continued through the morning of surgery

All patients received oral lorazepam (1-2 mg), morphine (0.1 mg/kg IM), and scopolamine (0.3-0.4 mg IM) 2 hours before induction of anesthesia. Patients were continuously monitored utilizing a twolead electrocardiogram (leads II and V₅), and central venous, pulmonary-artery, and radial artery catheters. Catheter placement was facilitated by the use of 1% lidocaine without epinephrine for local anesthesia. Additionally, during catheter placement, lorazepam (1-2 mg IV) was administered for further sedation. Patients then breathed oxygen at a Flo2 of 1.0, and anesthesia was induced with fentanyl (150 μ g IV) and lorazepam (4 mg IV). After induction of anesthesia as indicated by loss of lid reflex, ventilation was controlled using a facemask and a pharyngeal airway throughout the period of study.

Two minutes after the induction of anesthesia, baseline hemodynamic measurements were made and the muscle relaxant was administered intervenously as a bolus. Group 1 patients received attacurium 0.5 mg/kg, group 2 patients received vecuronium 0.12 mg/kg. Hemodynamic measurements were

then repeated at 2, 5, and 10 minutes after the drug was administered. Samples for measurement of arterial blood gas tensions and serum histamine levels were obtained at the same times. Hemodynamic variables measured included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Iced 5% dextrose in water and an Edward's Cardiac Output Computer, model 9510A, were used to measure cardiac output, the final value being determined by calculating the mean of duplicate thermodilution values. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated from the above data using the standard formulas. Serum histamine levels were determined by a radioenzymatic analysis using High Specific Activity Tritiated H-Methyl S-adenosylmethionine and purified histidyl-N-methyltransferase (HNMT).

Analysis of the data was performed using a two-way analysis of variance, Student's t-tests for paired and grouped data (with the Bonferroni correction for multiple comparisons), and linear regression. Statistical significance was set at P < 0.05.

Results

Results in groups 1 and 2 are shown in Tables 1 and 2, respectively. Analysis of the data revealed statistically significant hemodynamic changes which show that in group 1 (atracurium) systolic and diastolic blood pressures decreased significantly below baseline values 2 minutes after bolus injection of the drug. Additionally, cardiac output increased significantly over baseline levels 2, 5, and 10 minutes after the bolus of atracurium. These increases in cardiac output were associated with significant decreases in systemic vascular resistance. Pulmonary capillary wedge pressure was also decreased significantly be-

tP < 0.05 from baseline.

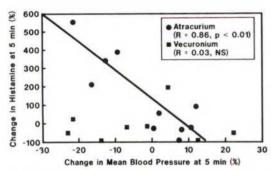
Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure.

Table 2. Group 2: Vecuronium 0.12 mg/kg

	Baseline	2 min	5 min	10 min
HR (beats/min)	57.8 ± 4.4*	57.5 ± 3.8	55.9 ± 3.9	56.3 ± 4.2
SBP (systolic - mm Hg)	133.8 ± 7.6	129.5 ± 4.8	129.8 ± 5.3	125.1 ± 5.6
DBP (diastolic - mm Hg)	65.1 ± 3.2	61.9 ± 2.7	61.8 ± 2.3	60.5 ± 2.2
CO (liters/min)	4.31 ± 0.34	4.63 ± 0.35	4.24 ± 0.43	4.26 ± 0.41
SVR (dynes-sec-cm ⁻⁵)	1444 ± 111	1352 ± 133	1604 ± 256	1473 ± 142
PCWP (mm Hg)	16.1 ± 1.7	13.8 ± 1.2	13.3 ± 1.0	$12.3 \pm 1.2 \dagger$
% Change histamine from baseline	0*	-17.0 ± 15.6	-12.1 ± 32.5	-45.1 ± 14.1

*Mean ± se; *n* = 10. †*P* < 0.05 from baseline. Abbreviations as in Table 1.

Histamine and Blood Pressure



<u>Figure 1</u>. Changes in histamine levels in individual patients correlate strongly with changes in blood pressure for patients in the atracurium group (group 1), but no correlation exists between changes in histamine levels and changes in blood pressure in the vecuronium group (group 2).

low baseline levels 5 and 10 minutes after injection of the drug. Patients in group 2 (vecuronium) showed no significant change from baseline values in any of the hemodynamic variables measured other than a statistically significant decrease in pulmonary capillary wedge pressure 10 minutes after the administration of the drug. No statistically significant differences between groups were found.

Tables 1 and 2 summarize data on percent changes in serum histamine levels from baseline in response to bolus injection of atracurium or vecuronium, respectively. In the atracurium group (Table 1), the percentage increase in serum histamine levels from baseline was statistically significant at each interval of measurement. The increases in serum histamine were associated with significant increases in cardiac output and decreases in systemic vascular resistance at each time point. With vecuronium (Table 2), no significant changes occurred in serum histamine levels. Figure 1 shows that the changes in an individual patient's serum histamine level correlated significantly to changes in mean arterial pressure 5-minutes after atracurium, whereas no such correlation existed after vecuronium.

The patients in groups 1 and 2 did not significantly differ from each other with respect to patient char-

acteristics such as age, sex, New York Heart Association Class, ejection fraction, left ventricular end diastolic pressure, medications, or baseline hemodynamic data. Baseline SVR appears to be somewhat higher in group 1 than in group 2. However, analysis of the data revealed that this difference is not statistically significant. Additionally, no electrocardiographic changes consistent with ischemia were noted in either group throughout the period of study. No statistically significant differences were noted between groups with respect to Po₂, Pco₂, pH, and bicarbonate. All patients were well oxygenated with a Pco₂ maintained between 35–45 mm Hg and pH in the 7.36–7.44 range throughout the study.

Discussion

Hemodynamic stability is an integral and essential goal of any anesthetic management plan in patients with cardiac disease. The importance of this stability in terms of patient outcome has recently been emphasized (5). In this study, equipotent doses (2.5 times the ED₉₅ for neuromuscular blockade) were utilized (6,7). Used within this clinical dose range, vecuronium produced fewer hemodynamic side effects than did atracurium. This is particularly true with respect to the lack of a statistically significant decrease in systemic vascular resistance and a reflex increase in cardiac output that was seen with atracurium. These results are similar to those found by Lennon et al. (8), who reported on the hemodynamic changes produced by doses of atracurium and vecuronium which were approximately six times the ED₉₅ for each drug. In that study, atracurium produced a decrease in mean arterial pressure of >20% within the first 60 seconds in 42% of patients given the drug (1.5 mg/kg). Vecuronium, on the other hand, produced minimal hemodynamic side effects in patients receiving an equipotent dose (0.25 mg/kg). The authors (8) went on to report that blood pressure after intubation increased in the vecuronium group but remained

decreased in the group given atracurium. They attributed these changes in the vecuronium group to the intubation stimuli, whereas they believed that the hemodynamic side effects of atracurium more than counteracted the hypertensive response to laryngoscopy. The hemodynamic data were not obtained after tracheal intubation in the present study. The patients were ventilated by facemask throughout the period of study, after which they received a high-dose fentanyl (50 μ g/kg IV) anesthetic before tracheal intubation. In this way, the hemodynamic consequences of tracheal intubation under light anesthesia were avoided.

The undesirable cardiovascular changes produced by nondepolarizing muscle relaxants may be secondary to histamine release, ganglionic blockade, cardiac antimuscarinic effects, and/or sympathomimetic effects. As shown in Tables 1 and 2, and in Figure 1, the hemodynamic effects produced by atracurium correlated well with increases in serum histamine levels. However, Figure 1 illustrates that there is marked variability with respect to the degree to which histamine levels increased after the injection of atracurium. This agrees with the findings of Philbin et al. (3), who suggested that a small portion of the population is capable of releasing large amounts of histamine after receiving doses of atracurium even lower than the dose used in this study. The hemodynamic data are also consistent with the finding of other investigations that intubating doses of atracurium, when administered as a bolus, are associated with statistically significant hemodynamic effects (7,9).

The undesirable consequences of histamine release on the cardiovascular system are well known and have been summarized (10). The inotropic, chronotropic, antidromic, and coronary artery flow effects of histamine in the human myocardium have been demonstrated (9). In addition, histamine may lower the threshold for ventricular fibrillation and may contribute to the generation of malignant arrhythmias. Moss and Rosow (10) suggest that drugs with histamine-releasing properties be used with caution in patients known to have arrhythmias. The peripheral vasculature also responds to increased blood levels of histamine with vasodilation and increased vascular permiability. Hence, drugs with marked histamine releasing properties are undesirable in the cardiac surgical patient. These and other undesirable effects of histamine release have been described by Siler et al. (11), who reported on a case of a 34-yearold, ASA I woman who developed hypotension, tachycardia, and bronchospasm after an intravenous bolus of atracurium.

The results of this study reveal that vecuronium is

free of significant hemodynamic side effects at the dose used. This is in agreement with the work of Morris et al. (1), who found minimal hemodynamic effects from a dose of vecuronium almost three times that utilized in this study. However, Figure 1 also illustrates that, although it is not as marked as with atracurium, there is variability in the hemodynamic responses of individual patients to a vecuronium bolus. The etiology of this variability is not immediately clear. Figure 1 shows that the decrease in mean arterial pressure seen in some patients secondary to vecuronium does not correlate with changes in serum histamine levels. Sutherland et al. (12) have suggested that large doses of vecuronium may possess ganglionic blocking activity. Although this may be a possible, if only partial, explanation the reason for the patient variability remains to be elucidated. However, the data in Table 2 illustrate that although patient variability occurs, it is not enough to produce significant hemodynamic alterations in response to vecuronium.

Are the statistically significant hemodynamic effects produced by an intubating dose of atracurium of clinical significance? In this patient population, as well as in the majority of patients with a normally functioning myocardium, the answer is probably no. Despite the fact that all the patients had significant coronary artery disease, no patient developed electrocardiographic changes consistent with ischemia. Although the possibility of early ischemia and wall motion abnormalities was not excluded, the hemodynamic changes produced by atracurium were transient and clinically well tolerated by all patients, all of whom had normal postoperative recoveries. However, it must be remembered that all patients under study had normal ventricular function. Hence, when the systemic vascular resistance decreased, they could respond by increasing cardiac output, thus attenuating the decrease in systemic blood pressure. Although not determined by this study, the real clinical significance of the hemodynamic sequelae resulting from histamine release produced by an intubating dose of atracurium might be seen in patients with poorly functioning myocardiums. The "sick" myocardium may not have the reserve adequate to increase cardiac output in response to the inotropic effects of histamine and the decrease in systemic vascular resistance. In this situation, the decrease in blood pressure could be more marked than that seen in the present study.

Many factors play a role in the determination of the muscle relaxant utilized in the surgical patient. These include duration of action, route of metabolism, cost, physical status of the patient (in particular the myocardium) and/or the histamine releasing capability of the agent to be used, and the hemodynamic consequences of such release. Hemodynamic stability is important in the anesthetic management of any patient. If the patient has known cardiovascular disease or is critically ill, hemodynamic stability becomes even more important and may be crucial in determining the eventual outcome. From our data we conclude that when utilizing the above clinical dose range, use of vecuronium may be advantageous over use of atracurium. This is particularly true in the patient with cardiac disease in whom the cardiovascular sequelae of histamine release are undesirable.

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Reproductive and Teratogenic Effects of Sufentanil and Alfentanil in Sprague-Dawley Rats

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The reproductive and teratogenic effects of sufentanil and alfentanil were studied in a total of 168 Sprague-Dawley rats in two separate experiments. Either sufentanil (10, 50, or 100 µg·kg⁻¹·day⁻¹) or alfentanil (8 mg·kg⁻¹·day⁻¹) were administered continuously from day 5 through day 20 of pregnancy using subcutaneously implanted osmotic min-

ipumps. Cesarean sections were performed on day 20 of pregnancy, reproductive indexes were determined, and the 1484 fetuses were examined for external, visceral, and skeletal abnormalities. No significant adverse reproductive or teratogenic effects were observed with either narcotic.

Key Words: NARCOTICS—sufentanil, alfentanil. PREGNANCY, TERATOGENICITY—sufentanil, alfentanil. TOXICITY, REPRODUCTIVE—sufentanil, alfentanil.

For the past 10 years we have studied the reproductive and teratogenic effects of the inhaled anesthetics in several rodent models (1–8). Until recently, reliable studies of parenteral anesthetic agents and narcotics were not possible because of the extensive maternal toxicity associated with bolus administration of even relatively low doses of these drugs. The use of chronically implanted subcutaneous (SC) osmotic minipumps has, however, permitted delivery of high total daily doses of local anesthetics and narcotics at a constant rate throughout organogenesis without causing adverse maternal physiologic effects. Thus, we have studied lidocaine and fentanyl and found that they are devoid of adverse reproductive effects (9,10). In the present study, we have extended our reproduction and teratology investigations of parenteral agents to include the new narcotics, sufentanil and alfentanil.

Methods

Timed pregnant Sprague-Dawley rats were received from the breeder (Hilltop Lab Animals, Inc., Scott-

dale, PA) either on day 2 (sufentanil experiment) or on day 4 of pregnancy (alfentanil experiment), weighed, and identified with metal ear tags. (Day 0 of pregnancy was defined as the day a copulatory plug was observed in the vagina.) Rats were bedded on ground corncob (Bed-O'Cobs, Anderson's Cob Division, Maumee, OH), housed four per cage and fed standard laboratory rodent food (Wayne Lab Blox, Allied Mills, Inc., Chicago, IL) and tap water ad libitum. Temperature in the animal room was maintained at 21–24°C and artificial light was provided from 6 AM to 7 PM each day. Care of rats was in accordance with institutional guidelines.

Two separate experiments of similar design were performed. In each experiment, on day 5 of pregnancy, an osmotic minipump with a 15-day drug supply (Alzet miniosmotic pump, model 2ML2, 5 μ l/hr delivery rate, Alza Corp., Palo Alto, CA) was implanted SC in the back of each rat (11). To accomplish the procedure, which took less than 1 minute to complete, general anesthesia was induced with an IM injection of 0.3 ml/kg of a mixture containing ketamine 60 mg/ml, xylazine 6 mg/ml, and acepromazine, 1.2 mg/ml. In the first experiment, 128 rats were assigned to four groups of approximately equal average weight and were treated with either: 1) saline (control; n=39); 2) a low dose of sufentanil (10 μ g·kg⁻¹·day⁻¹; n=30); 3) an intermediate dose of

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Table 1. Summary of Group Body Weight and Body Weight Changes*

		Sufe	entanil (μg/kg per	day)		Alfentanil (mg/kg per day
Group	Control	10	50	100	Control	8
No. of rats studied	39	30	30	29	20	20
Body weight						
On arrival from breeder	202 ± 16	202 ± 14	203 ± 16	201 ± 14	204 ± 14	207 ± 12
Day 11 of pregnancy	244 ± 15	245 ± 14	242 ± 17	241 ± 14	265 ± 16	268 ± 19
Day 20 of pregnancy (day of cesarean section)	342 ± 28	347 ± 23	332 ± 40	327 ± 38	359 ± 23	345 ± 32

^{*}Values are in grams (mean ± sp).

sufentanil (50 μ g·kg⁻¹·day⁻¹; n = 30); or 4) a high dose of sufentanil (100 μ g·kg⁻¹·day⁻¹; n = 29). In the second experiment, 40 rats were allocated to two groups and were treated with either; 1) saline (control; n = 20); or 2) a high dose of alfentanil (8 $mg \cdot kg^{-1} \cdot day^{-1}$; n = 20). Sufentanil and alfentanil solutions were prepared from citrate powders (Janssen Pharmaceutica, Piscataway, NJ) dissolved in normal saline. Dosages of the narcotics were based on data from preliminary studies in which we determined the highest dose that did not cause maternal weight loss. In our experience with narcotics delivered with osmotic minipumps, maternal weight loss consistently occurs before respiratory depression. Only the highest dose of alfentanil was studied with the intention of studying lower doses if the single dose gave positive results. Rats were weighed every 2–3 days during the experiment.

On day 20 of pregnancy, 1 day before the expected delivery date, rats were killed by carbon dioxide inhalation and cesarean section was performed. The uterus was examined and the number and position of live and dead fetuses, resorptions, and implantations were recorded. The weight and sex of each live fetus were determined and all fetuses were examined for external abnormalities. Every other fetus was fixed in 70% ethanol and macerated with potassium hydroxide. The skeleton was then stained with alizarin red S using the modified method of Staples and Schnell (12), cleared with glycerol, and subsequently examined microscopically for skeletal abnormalities. The remainder of the fetuses were preserved in Bouin's solution and subsequently dissected and examined microscopically for visceral abnormalities as described by Barrow and Taylor (13). All examinations were done without knowledge of the treatment groups.

Abnormalities were classified as follows. Fetal morphologic abnormalities that alter general body conformation, disrupt or interfere with bodily func-

tions, or generally appeared to be incompatible with life were categorized as major malformations. Abnormalities in anatomic structure that were considered to have no significant biological effect on animal health or body conformity and represented only slight deviations from normal were categorized as developmental variants. Abnormalities that did not fall under the strict definition of major malformations but which were clearly not developmental variants were categorized as minor anomalies.

Statistical Analysis

The percentage of abnormal fetuses in each litter of each treatment group was computed and group means were compared with control group means by one-way analysis of variance (ANOVA). Student's t test, corrected for multiple comparisons (Bonfferoni), was used as an a posteriori test when differences were found with ANOVA. P < 0.05 was considered statistically significant.

Results

Maternal Effects

No rats treated with sufentanil died during the experiment. Four rats treated with alfentanil died, one on each of the first 4 days after pump implantation. Otherwise, no adverse effects were observed during the experiments. There were no differences in weight gain among any of the groups in either experiment (Table 1).

Reproductive Effects

There were no significant differences among the groups in pregnancy rate, total number of implanta-

Table 2. Maternal and Fetal Observations at Cesarean Section on Day 20 of Pregnancy*

		Safe	entanil (µg/kg per	day)		Alfentanil (mg/kg per day)	
Group	Control	10	50	100	Control	8	
No. of rats studied	39	30	30	29	20	20‡	
No. of rats pregnant	34	25	22†	26 †	18	11	
Pregnancy rate (%)	87	83	<i>7</i> 3	90	90	69	
No. of implantations/rat	11.9 ± 2.4	12.0 ± 2.0	12.0 ± 2.0	11.5 ± 2.0	11.7 ± 2.0	11.3 ± 2.9	
No. of live fetuses/rat	11.6 ± 2.4	11.8 ± 1.9	11.4 ± 1.8	10.7 ± 2.4	11.2 ± 2.0	9.8 ± 4.2	
Percent fetal wastage/rat (%)	2.5 ± 4.5	1.6 ± 3.9	5.1 ± 7.0	7.1 ± 9.2	3.7 ± 5.5	11.5 ± 24.8	
Percent female/rat (%)	49.3 ± 11.0	$53.2 \pm 15.I$	52.1 ± 13.1	49.1 ± 14.8	44.1 ± 17.7	$60.0\$ \pm 19.5$	
Mean fetal weight (g)	4.5 ± 0.2	4.6 ± 0.2	4.7 ± 0.3	4.7 ± 0.3	4.6 ± 0.5	4.3 ± 0.3	

^{*}Mean ± sp.

Table 3. Summary of Fetal Examination

		Sı	ufentanil (<i>µ</i> /kg/da	y)		Alfentanil (mg/kg per day)	
Group	Control	10	50	100	Control		
No. of rats examined	34	25	20	24	18	11	
External examinations							
No. of fetuses examined	394	29€	227	257	202	108	
Any abnormalities (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Runt (%)	0.2 ± 1.4	0.4 ± 2.0	0.0 ± 0.0	0.3 ± 1.4	0.6 ± 2.4	3.5 ± 6.6	
Visceral examinations							
No. of fetuses examined	198	148≣	112	130	100	53	
Major malformations (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Minor anomalies (%)	7.9 ± 13.5	2.2 ± 5.0	5.0 ± 7.8	3.9 ± 7.9	5.2 ± 8.9	3.1 ± 6.6	
Skeletal examinations							
No. of fetuses examined	196	148≛	115	127	102	55	
Major malformations (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Minor anomalies (%)	0.0 ± 0.0	1.1 ± 3.9	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 4.0	0.0 ± 0.0	
Developmental variants (%)	25.5 ± 23.5	34.0 ± 32.0	32.3 ± 28.3	30.5 ± 27.7	16.8 ± 22.6	33.9 ± 31.8	

Mean percentage abnormal fetuses per rat ± sp

tions and live fetuses, percent fetal wastage per litter, or mean fetal weight (Table 2). There were more female offspring in the alfentanil group than in the control group, the difference achieving statistical significance in part due to the lower than usual percentage of male offspring in the control group.

Teratogenic Effects

A total of 1174 offspring were delivered from the 107 pregnant rats and all were examined for external abnormalities. Subsequently, 588 fetuses were examined for visceral and 586 for skeletal abnormalities. The results of these examinations are shown in Table 3. There were no significant teratologic findings in any group.

Discussion

In the present study, we tested the reproductive and teratogenic effects of the narcotics, sufentanil and alfentanil, and found both agents to be benign. In this respect, our results are similar to those we obtained with the parent compound in this series, fentanyl (10). We found that fentanyl in doses up to 500 μ g·kg⁻¹·day⁻¹, delivered with osmotic minipumps for 2 weeks before breeding and during the entire period of pregnancy, was devoid of adverse reproductive effects. In another study, adding 500 μ g·kg⁻¹·day⁻¹ of fentanyl to 50% N₂O did not increase the teratogenic effects of 50% N₂O alone (14). However, our results differ from those of studies of the older narcotics, morphine, meperidine and methadone, in which adverse reproductive effects gener-

[†]Two rats were pregnant but had no live fetuses.

[‡]Four rats died before day 20.

 $[\]S P < 0.05 \text{ vs control}.$

ally were reported at high doses (15–19). In these other investigations, narcotics were given once or twice daily by various parenteral routes. From the doses and side effects reported in these other studies, and from our own studies (10), we surmise that the test animals experienced respiratory depression. Thus, it is difficult to compare our results with the new narcotics with those of past studies because the design of the older studies almost certainly was flawed.

Apart from avoiding respiratory depression and the thoracic rigidity associated with administration of high doses of narcotics, there are other advantages to using osmotic pumps for reproduction and teratology studies. It is common in studies such as the present one to administer the test drug throughout the period of organogenesis, days 6-15 of gestation in the rat. For agents that cannot be administered orally or by inhalation, this necessitates daily injections. The handling and trauma associated with multiple injections can in themselves be confounding experimental factors. Another problem with administration of bolus doses of narcotics is that, with a relatively short half-life, withdrawal may occur between doses. In fact, Lichtblau and Sparber (20) have suggested that in utero withdrawal from narcotics was more detrimental to the rat fetus than was continued exposure. By using chronically implanted SC osmotic minipumps, constant plasma levels of test agent can be maintained from day 5, the day before implantation, until day 20, the day before parturition, when rats are killed.

In terms of experimental design, the cost of using SC-implanted osmotic minipumps is small. Although general anesthesia is required to insert the pumps, the procedure is quick and relatively noninvasive. Also, Nau et al. (21) have reported that the total daily dose of a given agent (valproic acid) required to produce embryotoxicity was approximately ten times higher when it was delivered with SC-implanted osmotic pumps than by injection. Assuming the same ratio applies to narcotics, the amount of narcotic that can be delivered with osmotic minipumps without causing adverse maternal effects is still far in excess of the amount that can be safely delivered by injection, i.e., approximately 100:1 for fentanyl (10).

In conclusion, sufentanil and alfentanil do not cause adverse reproductive or teratogenic effects in rats when administered throughout organogenesis with SC-implanted osmotic minipumps. From a methodologic point of view, osmotic minipumps facilitate study of the reproductive and teratogenic effects of narcotics as they permit delivery of dosages that would not be tolerated by bolus injection or might otherwise confound experimental design.

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Systolic Pressure Variation Is Greater during Hemorrhage than during Sodium Nitroprusside-Induced Hypotension in Ventilated Dogs

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PIZOV R, YA'ARI Y, PEREL A. Systolic pressure variation is greater during hemorrhage than during sodium nitroprusside-induced hypotension in ventilated dogs. Anesth Analg 1988;67:170–4.

The systolic pressure variation (SPV), which is the difference between the maximal and minimal values of the systolic blood pressure (SBP) after one positive-pressure breath, was studied in ventilated dogs subjected to hypotension. Mean arterial pressure was decreased to 50 mm Hg for 30 minutes either by hemorrhage (HEM, n=7) or by continuous infusion of sodium nitroprusside (SNP, n=7). During HEM-induced hypotension the cardiac output was significantly lower and systemic vascular resistance higher compared with that in the SNP group. The systemic, central venous, pulmonary capillary wedge pressures, and heart rates, were similar in the two groups. Analysis of the

respiratory changes in the arterial pressure waveform enabled differentiation between the two groups. The SPV during hypotension was 15.7 \pm 6.7 mm Hg in the HEM group, compared with 9.1 \pm 2.0 mm Hg in the SNP group (P < 0.02). The Δ down, which is the measure of decrease of SBP after a mechanical breath, was 20.3 \pm 8.4 and 10.1 \pm 3.8 mm Hg in the HEM and SNP groups, respectively, during hypotension (P < 0.02). It is concluded that increases in the SPV and the Δ down are characteristic of a hypotensive state due to a predominant decrease in preload. They are thus more important during absolute hypovolemia than during deliberate hypotension.

Key Words: BLOOD PRESSURE—shock and induced hypotension. ANESTHETIC TECHNIQUES—induced hypotension. SHOCK—systolic blood pressure.

A single positive-pressure breath normally affects the arterial waveform in a biphasic manner. The blood pressure increases during early inspiration and later decreases during late inspiration and early expiration (1). The difference between the maximal and minimal values of the systolic blood pressure (SBP) after one mechanical breath was termed by us the Systolic Pressure Variation (SPV) (2) (Fig. 1). The SPV can be further divided into two components, the Δ up and the Δ down, by using the systolic blood pressure after a short apnea (2) or during the preinspiratory period (3) as a reference value (Fig. 1). The Δ down is the difference between the SBP during apnea (SBPapn)

and the lowest value of the SBP after a mechanical breath. Its magnitude reflects the amount of decrease in the venous return due to the increased intrathoracic pressure (4).

The Δ up is the difference between the maximal value of the SBP and the SBPapn (Fig. 1). The Δ up represents a transient increase in the left ventricular stroke output due to a combination of increased preload as blood is squeezed out of the lungs, decreased afterload, direct pressure of the expanding lungs on the heart, and improved left ventricular compliance due to a transient decrease in the volume of the right heart (5–7).

Recently we have quantified the SPV during graded hemorrhage in ventilated dogs and found it to be a more sensitive indicator of latent hypovolemia compared with other hemodynamic parameters (2). Thus the more hypovolemic the dogs became, the higher was their SPV, mainly because of an increase in the Adown component. The early diagnosis of such latent hypovolemia is of obvious importance because it ensures adequate fluid administration and

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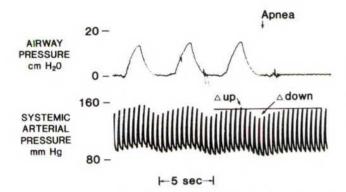


Figure 1. Airway and arterial pressures during mechanical ventilation and apnea. The systolic blood pressure during apnea serves to divide the SPV into Δ up and Δ down components.

prevents the development of a low flow state. This is especially true during intraoperative deliberate hypotension, a technique that uses vasodilators to decrease systemic blood pressure electively. This technique is used in operations in which considerable blood loss is anticipated or in which a blood-free surgical field is crucial. The technique of controlled hypotension aims to lower the blood pressure while maintaining normal cardiac output and organ perfusion. Although the mean blood pressure is lowered to about 50 mm Hg, considerable blood loss can still occur during the procedure. Intraoperative deliberate hypotension can thus result from the synergistic effects of vasodilatation and reduction of the absolute blood volume. As the SPV has been shown to be a useful indicator of hypovolemia, we have examined its ability to differentiate hypotension due to hemorrhage from that induced by sodium nitroprusside.

Materials and Methods

Fourteen dogs weighing 15.2 ± 3.8 kg (mean ± sd) were anesthetized with intravenous pentobarbital 30 mg/kg, their tracheas were intubated, and they were paralyzed by a continuous intravenous infusion of succinylcholine 0.01 mg/kg per min. The dogs' lungs were ventilated by a constant volume ventilator (Harvard pump, Dover, MA.) with a tidal volume (VT) of 12 ml/kg, at a rate of 14–16 breaths/min to keep their Paco₂ within normal values (40 ± 5 mm Hg). Inspired gas included 30% oxygen, 69% room air, and 1% halothane. Occasional metabolic acidosis was corrected with sodium bicarbonate to normalize arterial pH throughout the preparatory cannulation.

A 16-g Teflon catheter was inserted into the femoral artery and a pulmonary arterial balloon-tipped catheter (7F, Instrumentation Laboratories, Lexington, MA.) was floated through the external jugular

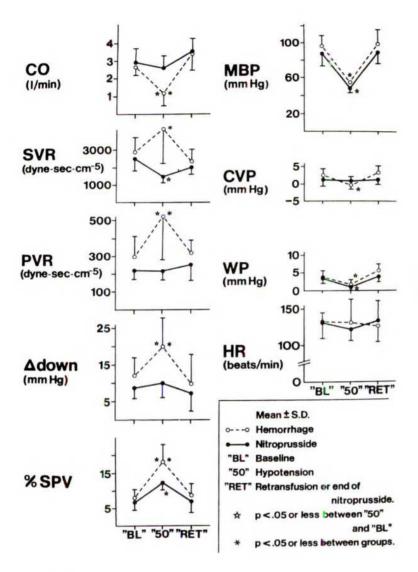
vein for the measurement of central venous (CVP) pulmonary artery and pulmonary capillary wedge (WP) pressures as well as cardiac output (CO). An 8F catheter with additional side holes was inserted into the pleural space through the fifth intercostal space at the right midaxillary line for measurement of pleural pressure. Airway pressure was measured through an opening in the endotracheal tube situated close to its tip. The airway and the pleural pressure lines were filled with normal saline and connected to Statham P23AA transducers. Systemic and pulmonary arterial catheters were connected to Gould Statham P23Db transducers. All pressure waveforms were recorded continuously on a four-channel Grass Polygraph (Grass Instruments, Quincy, MA.).

Lung (CL) and chest-wall (Ccw) compliances were measured by slow inflation of 300 ml of air with a precalibrated syringe after which airway (Paw) and pleural (Ppl) pressures were measured during a 2-second inspiratory hold. The Ccw and CL were calculated as VT/ Δ Ppl and VT/(Δ Paw – Δ Ppl), respectively. Because the compliance of the chest wall relative to lung compliance in dogs is usually higher than that of humans (8), we inflated a vest situated around the dog's chest so that the mean CL/Ccw ratio was kept 1.01 \pm 0.23, which is the normal ratio for humans (9). The level of vest inflation was kept constant throughout the experiment.

The SPV was measured from the paper chart as the difference between the maximal and the minimal SBP during one mechanical breath, and the mean value during five consecutive breaths was calculated. The Δ up and Δ down components of the SPV were measured relative to the SBPapn (Fig. 1) and the %SPV was calculated as the ratio between SPV and SBPapn \times 100.

Cardiac output was measured by triplicate injections of 5 ml iced-saline using the IL cardiac output computer (model 701, Lexington, MA.). All injections were done at the same time during early expiration. Systemic (SVR) and pulmonary (PVR) vascular resistances were calculated using standard formulas.

In seven dogs (SNP group) the mean blood pressure was decreased to 50 mm Hg by a continuous infusion of SNP (17.4 \pm 4.2 μ g/kg per min). Constant hypotension was maintained for 30 minutes, after which SNP was stopped. In the other seven dogs (HEM group), mean blood pressure was decreased over 30 minutes to 50 mm Hg by bleeding through the femoral artery catheter into a plastic bag containing CPDA-1. After an additional 30 minutes of hypotension, the shed blood (689 \pm 227 ml) was retransfused. All variables were measured at baseline, after 30 minutes of hypotension, and 15 minutes after



<u>Figure 2</u>. Hemodynamic parameters during baseline, hypotension, and recovery in the hemorrhage and the sodium nitroprusside groups.

either the end of retransfusion or the cessation of SNP.

The variables were compared at the end of the hypotensive period and at the end of the retransfusion period to baseline values within each group, using the Wilcoxon matched-pairs nonparametric test. Variables at baseline, hypotension, and retransfusion were compared between the groups using the Mann-Whitney nonparametric test. P < 0.05 was considered to be statistically significant. All data is presented as mean \pm sp.

Results

The baseline values of hemodynamic variables and CL/Ccw ratios were similar in both groups (Fig. 2). SNP-induced hypotension was associated with a significantly lower SVR and WP compared with base-

line, while CVP, heart rate (HR), PVR, and cardiac output remained unchanged. The SPV (8.4 ± 2.6 and 9.1 ± 2.0 mm Hg during baseline and hypotension, respectively), Δ up, and Δ down remained unchanged as well, but the %SPV increased from 7.1 ± 2.2 to $12.5 \pm 2.2\%$ (P < .001) during SNP infusion.

During hemorrhage-induced hypotension, the CO, CVP, and WP decreased significantly (Fig. 2), while PVR (P < 0.001) and SVR (P < 0.078) increased. The mean SPV increased after hemorrhage from 12.6 \pm 3.7 to 15.7 \pm 6.7 mm Hg. This difference was not statistically significant as the SPV increased in only six dogs of the HEM group. In the seventh dog, the maximal SBP never reached the level of the apneic SBP during hemorrhage (Fig. 3). Thus, although the blood pressure seemed to be even more depressed by positive pressure ventilation in that dog, the negative Δ up-value did artificially decrease the SPV. The %SPV and the Δ down of the HEM group increased

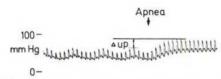
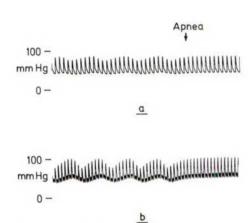


Figure 3. The arterial waveform of one dog of the HEM group showing continuous depression of the arterial pressure during mechanical ventilation with partial recovery during apnea. Note uncharacteristically negative Δ up.



<u>Figure 4</u>. Two characteristic arterial waveforms during hypotension: (a) SNP; (b) HEM; Note increased respiratory changes of the systolic blood pressure, i.e., increased SPV during HEM.

significantly during hemorrhage while the Δ up was variable and changed from 0.4 ± 3.2 during baseline to -4.6 ± 7.5 mm Hg during hemorrhage. During hemorrhage the hematocrit decreased from 36.3 ± 5.4 to $32.3 \pm 5.3\%$.

Although the mean blood pressure, HR, CVP, and WP were the same in both groups during hypotension, the HEM group had a significantly lower cardiac output, significantly higher SVR, PVR, Δ down, and %SPV as compared with the SNP group (Fig. 2). The SPV itself was also significantly higher during hypotension in the HEM group (15.7 \pm 6.7 mm Hg) compared with that of the SNP group (9.1 \pm 2.0 mm Hg, P < 0.02). Two examples of characteristic arterial pressure waveforms are shown in Fig. 4. After retransfusion or cessation of SNP, all variables returned close to their baseline values and showed no difference between the two groups (Fig. 2).

Discussion

The hemorrhage-induced hypotensive state is characterized by low cardiac output and high systemic vascular resistance (10). During hypotension induced by SNP, the cardiac output usually remains normal while the systemic vascular resistance is low (11,12). Although these two hypotensive states are different

from each other, this difference cannot be identified by commonly measured hemodynamic variables. The blood pressure, heart rate, CVP, and even the WP, were similar during hypotension in both the HEM and the SNP groups. However, analysis of the respiratory variations in the systolic blood pressure did show differences between the two groups.

The hypotension that occurs during SNP administration is produced by a reduction of both preload and afterload, as the effective blood volume decreases and the vascular bed dilates at the same time. Compared with the same degree of hypotension during hemorrhage, the preload during SNP is reduced to a lesser extent, which is the reason why the Δ down was different between the two groups. The Δ down component of the SPV reflects the decrease in left ventricular preload after a mechanical breath. It has been shown by us to reveal occult hypovolemia in the presence of normal values of MBP, HR, CVP and WP, and to correlate best with the CO during moderate hemorrhage. It is therefore obvious that it should be more pronounced in situations in which hypotension is due to compromised preload alone. Because the Δdown is the main component of the SPV during hemorrhage, the SPV itself was also higher during hemorrhage. However, the SPV may not have reflected fully the decreased preload because, at times, the systolic blood pressure during positive-pressure ventilation never reached the value of the systolic pressure during apnea. This may happen when the venous return is extremely compromised, when the respiratory rate is very high so that the cardiac output does not recover before the next breath, or in the presence of airtrapping. An example of a relatively low SPV due to a negative Δ up was demonstrated in one of the dogs of the HEM group (Fig. 3). Thus, further division of SPV into Δup and Δdown components by the introduction of a short apnea is useful. Using the preinspiratory systolic pressure as a reference point (3) may be misleading because one cannot be sure that the left ventricular output has recovered by that time.

The %SPV may be a better index than the SPV because it relates the SPV to the absolute level of the systolic blood pressure during apnea. Thus an SPV of 20 mm Hg in the presence of a systolic blood pressure of 80 mm Hg during apnea (%SPV equals 25%) is more important than an SPV of 20 mm Hg associated with a systolic blood pressure of 160 mm Hg during apnea (%SPV of 12.5%).

A high SPV can also occur for reasons other than an absolute reduction in venous return. High tidal volume (13), decreased chest wall compliance, increased lung compliance, and arrhythmias (14) may all produce high SPV due to an increased Δ down. The SPV can also be increased by an increase in the Δ up during congestive heart failure associated with phasic increases of intrathoracic pressure (15).

Analysis of the respiratory-induced changes in the arterial waveform can be helpful in gaining insight into the hemodynamic status. This is especially true in situations in which hypovolemia cannot be diagnosed otherwise. The CVP and WP are measurements of pressure rather than volume and hence change little during further decreases of an already low preload because of the high ventricular compliance at these volumes (16). Thus, although CVP decreased significantly in the HEM group during hypotension, the absolute decrease was very small. Making therapeutic decisions on the basis of reductions of CVP or WP in the order of 2 mm Hg is impractical in clinic practice. Following the heart rate as a sign of tachycardia is quite nonspecific. In our model the dogs had a baseline tachycardia that is characteristic of this species during anesthesia. The decrease in the preload was reflected to a much greater extent by the Adown, which could differentiate between SNP- and hemorrhage-induced hypotension.

The respiratory variations in the arterial waveform may be different in dogs from humans, even though our dogs had a modified CL/Ccw ratio. However, we have recently completed a clinical study in which the SPV and its components were similar in patients during deliberate hypotension to those in our present experimental model, except that the Δup component in humans is more pronounced than in dogs. (Pizov R, Segal E, Perel A, unpublished data.)

Because we have not included a group of animals in which we combined SNP infusion and hemorrhage, we cannot conclude that any increase in the Δdown during the maintenance of the hypotensive state should be regarded as significant absolute hypovolemia. However, our previous experimental work (2), the present study, and our clinical data, lead us to believe in the consistency and validity and sensitivity of the SPV and its components as hemodynamic variables that may be useful in detecting occult hypovolemia.

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Inadvertent Subdural Injection:

A Complication of an Epidural Block

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Twenty-one hundred eighty two consecutive lumbar epidural injections were studied to determine the incidence of inadvertent subdural block retrospectively. A subdural block is defined as an extensive neural block in the absence of subarachnoid puncture, that is out of proportion to the amount of local anesthetic injected. Subdural injection is a complication of epidural block that probably occurs more frequently than previously recognized. An earlier report has estimated the incidence of subdural block to be 0.1%. This study, however, reports an incidence of 0.82% from a sample size of 2182 patients. Cadaveric dissection was also performed, further clarifying the presence and anatomic position of the subdural space.

Key Words: ANESTHETIC TECHNIQUES epidural.

It is generally accepted that the subdural space exists in the cerebral meninges. The potential extension of this subdural space, however, down into the spinal segment of the meninges has not been well appreciated. This subdural space can have clinical significance when local anesthetics are inadvertently deposited there, causing unexpected sensory, sympathetic, and motor blocks.

Clinically the extraarachnoid space has been demonstrated during myelograms with an incidence reported between 1 and 13% (1-3). This extraarachnoid subdural space lies between the dura and arachnoid membranes. It contains a small amount of serous fluid to moisten the surfaces of the opposing membranes. While not communicating with the subarachnoid space, the extra-arachnoid subdural space does continue for a short distance along the cranial and spinal nerves (4). It is larger in the cervical than in lumbar region, and is widest in its lateral and dorsal aspects (5). Here, there is free communication with the lymphatic vessels of the spinal nerves. Moreover, there are isolated connective-tissue trabeculae, especially on the posterior aspect, which contact the inside surface of the dura and the outside surface of the arachnoid.

Accidental subdural injections were first described by de Saram (6) and Dawkins (7), but no large series have examined its occurrence. There has been several case reports of accidental subdural catheterizations that have been radiographically confirmed (8-10). Dawkins' description of a "massive epidural" fits the clinical presentation of an inadvertent subdural injection. He describes an unexpected widespread nerve block occurring after a negative aspiration test associated with symptoms such as pupillary dilation, consistent with a high sympathetic block. In addition, the patients experienced a 20-minute delay in the onset of symptoms. This is in contrast to an accidental subarachnoid injection in which symptoms characteristically develop in 1-2 minutes. The purpose of this study is to retrospectively evaluate a large series of epidural injections to determine the incidence of inadvertent subdural block.

Methods

During the 30-month study period (March 1984-September 1986), 2182 lumbar epidural steroid injections were performed at the Pain Center for various forms of low back pathology. During this period any patient who exhibited any untoward or unpleasant

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side effects from the injection (e.g., headache, hypotension, nausea, motor or extensive sensory block) was identified for follow-up. The patients ranged in age from 17 to 86 years and each received a single epidural injection via a lumbar interspace, between L1 and L5. The blocks were performed by an attending anesthesiologist or a supervised resident using bupivacaine, 4-6 cc of 0.25% or 6-8 cc of 0.125%, in combination with methylprednisolone acetate 80-120 mg (Depo Medrol, Upjohn Company, Kalamazoo, Michigan). The epidural space was identified by the loss-of-resistance technique. After a careful negative aspiration test, injections were performed with disposable 17- or 18-gauge Touhy point needles. Aspiration was routinely done before, during, and after each injection. After the injections, the patients were observed for approximately 1 hour before discharge from the center.

Records were evaluated in the following manner for the presence or absence of clinical findings consistent with subdural injection. In any patient exhibiting a complication as mentioned above, a detailed description of the complication and clinical findings was obtained and recorded in the patient's chart at the time of occurrence. Clinical findings were classified into two levels of criteria, major and minor. Findings considered major criteria were: 1) a negative aspiration test, or 2) an unexpected widespread sensory block after epidural injection. The three minor criteria were: 1) a delayed onset of 10 minutes or more of a sensory or motor nerve block, 2) a variable motor blockade occurring, despite use of low doses of bupivacaine, or 3) sympatholysis out of proportion to the administered dose of local anesthetic. A positive subdural injection was judged to have occurred in both of the major criteria and at least one minor criteria were present. With the criterion of negative aspiration test we excluded any patient who had a wet tap before the apparent successful epidural injection. All of these records of morbid events were then retrospectively evaluated by one reviewer (TL) to determine if criteria for a subdural block were present. From 38 potential subdural injections, 18 were judged by an additional investigator (ADI) as having met the criteria for a subdural injection.

Results

Eighteen patients met the criteria for a subdural block, establishing an incidence of 0.82%. One patient exhibited all three minor criteria, while an additional seven patients displayed two of the minor criteria (Table 1).

All 18 patients developed sensory levels much higher than would be expected from the amount of local anesthetic administered. One patient had a sensory level of C4 after injection of 6 cc of 0.25% bupivacaine. In none of the 18 patients was CSF aspirated. Ten of the 18 patients developed motor block. Delayed onset times of greater than 10 minutes were noted in 11 patients (61%) with the longest time to onset of symptoms being 30 minutes. Hypotension, defined as a drop in systolic pressure of at least 30% from baseline, occurred in 11 patients. Eight of the 11 patients had moderate to severe hypotension with a drop in pressure greater than 40% of the baseline. Six of these patients had severe decreases in blood pressures. In all cases, hypotension responded to fluids or ephedrine (5-15 mg).

Five of the 18 patients (28%) had had previous back surgery. These five patients represent a higher percentage of patients than what is seen in our overall patient population (12%). Six of the 18 received 0.25% bupivacaine, while 12 received 0.125% bupivacaine.

Further studies were also performed on cadavers to provide additional information on the subdural space. The existence of the subdural space was confirmed by cadaveric dissection. A lumbar laminectomy was performed and the spinal cord and meninges were exposed from the S1 to the L1 levels. Dissected dura mater was found to have two layers: an outer, thicker, opaque layer and an inner, more translucent layer. Deep to these layers there existed a potential space easily identified after reflecting the dura mater. The arachnoid mater was noted to be a translucent membrane separating the subdural space from the subarachnoid space. Deep to the arachnoid mater the spinal nerves and subarachnoid space were identified. Our depiction of the anatomy is similar to the description made 23 years ago by Sechzer (11).

Discussion

Epidural nerve blocks occasionally exhibit an atypical pattern of spread. This may be caused by relative overdose or accidental injection into the subdural or subarachnoid spaces. Several investigators have demonstrated radiological confirmation of catheters present in the subdural space, especially in cases of "massive epidurals" (8,12). A recent report describes the ease of intentional subdural puncture and further suggests that accidental subdural puncture may occur in attempted epidural block even in experienced hands (13). Consequently, it appears that accidental subdural injection probably occurs more frequently than previously recognized.

Table 1. Summary of Patient Data

Patient no.	Bupivacaine concentration (%)	Vol.	Aspiration test	Level injected	Sensory level	Motor block	Degree of hypotension	Onset time (min)	Recovery time (hr)	Previous back surgery	Major criteria met	Minor criteria met
1	0.25	6	Neg	T12-L1	T4	Dense, LE bilateral	40%	10	3.5	Yes, fusion L4-5, 5-S1	2	2
2	0.25	4	Neg	L4-5	L2	Dense, LE bilateral	None	10	4.0	No	2	1
3	0.25	6	Neg	L3-4	T4	Moderate, LE bilateral	50%	10	3.0	No	2	2
4	0.125	8	Neg	L3-4	T2	Moderate, LE bilateral	50%	20	6.0	No	2	3
5	0.125	8	Neg	L3-4	T10	None	None	5	3.0	No	2	1
6	0.125	8	Neg	L3-4	T12	Mild LE bilateral	None	5	2.0	No	2	1
7	0.125	8	Neg	L3-4	Т6	Dense, LE bilateral	None	5	3.0	No	2	1
8	0.125	8	Neg	L3-4	T12	None	30%	30	2.0	No	2 2	2
9	0.125	8	Neg	L4-5	T8	None	50%	30	2.0	Yes, LAM X 2	2	2
10	0.125	8	Neg	L2-3	T10	Mild, LE bilateral	None	10	4.0	Yes, LAM	2	1
11	0.125	8	Neg	L3-4	L10	None	None	10	2.0	Yes, LAM	2	1
12	0.25	6	Neg	L3-4	T10	None	30%	5	1.5	No	2	1
13	0.125	8	Neg	L1-2	T6	None	40%	20	3.0	Yes, LAM	2 2	2
14	0.125	8	Neg	L4-5	T10	Dense, Le bilateral	None	5	3.0	No	2	1
15	0.125	8	Neg	L2-3	T4	Moderate, LE bilateral	50%	5	3.0	No	2	2
16	0.125	8	Neg	L3-4	Т9	Dense, LE bilateral	None	5	2.0	No	2	1
17	0.25	6	Neg	L4-5	C4	None	50%	10	3.0	No	2	1
18	0.25	6	Neg	L3-4	T2	None	50%	15	3.5	No	2	2

LAM, laminectomy; LE, lower extremity.

Intentional neurolytic subdural puncture has been previously described (14). This technique involves identification of the epidural space using the loss-of-resistance technique. The needle is then rotated through an arc of 180° with applied gentle pressure. In order to avoid accidental subdural puncture, the authors believe that a properly placed epidural needle should never be rotated to point the bevel in a superior or inferior position. If one rotates the needle to produce an intentional subdural puncture, this same practice, if repeated for an epidural block, may produce an accidental subdural puncture.

The three most common features noted in this study were: 1) an unexpectedly high sensory block, 2) exaggerated hypotension, and 3) unexpected motor block. An interesting characteristic of subdural blocks in the study is the variability in onset time. The fastest onset time was between 5 and 10 minutes, while other patients did not notice symptoms or exhibit signs until 30 minutes after injection. These findings do not differ significantly from other studies. Case reports have documented the onset of symptoms to be as long as 30 minutes. Other descriptions

of accidental subdural injections have reported onsets to be as short as 7 minutes (15). We believe that subdural blocks do exhibit a variability in onset time. This is dependent, perhaps, upon the relative amount of local anesthetic deposited in the subdural space, and may also be responsible for the widespread sensory block and exaggerated hypotension. Another explanation for the unexpected high sensory and sympathetic blocks may be that previous back surgery produced scarring and cicatrization, thereby partly obliterating the epidural space in the lower lumbar area. This partial obliteration of the epidural space may cause marked cephalad spread. There are, however, many exceptions to this hypothesis. Only 5 of the 19 patients had had previous back surgery. The patients who had the most dramatic symptoms (patients 3, 4, and 17) had had no back surgery. Three of the six patients who had previous back surgery (Patients 10, 11, and 13) were among those who exhibited the mildest symptoms. The presence of previous back surgery with deformity of the epidural space does not explain all of the observed events. However, it appears that patients who have had back

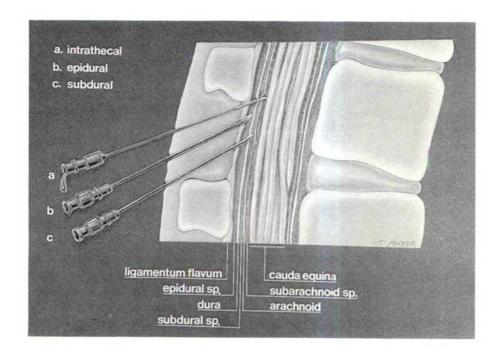


Figure 1. This illustration depicts relative position of intrathecal, epidural, and subdural needle placement. Note that if the needle is in the subdural space, with the dura straddling the bevel, some of the local anesthetic may be deposited in the subdural space while some will be placed in the epidural space.

surgery are more prone to accidental subdural injection. This is likely because the anatomy may be altered secondary to scarring and retraction, producing a thin epidural and wide subdural space.

Epidural blocks seem more likely to produce accidental subdural injection than do spinal blocks. This may be due to differences in technique and the type of needle used. Epidural injections use a large, blunttipped, long-bevel needle that is introduced very slowly, sometimes a millimeter at a time. In contrast, for a subarachnoid puncture, a thinner, sharper needle is introduced, usually at a much faster rate. It is more likely that the blunt needle tip will pierce the dura without piercing the arachnoid. The large opening of the epidural needle may straddle the subdural and epidural, allowing part of the local anesthetic to be injected into the subdural space while some of it could be deposited in the epidural space (Fig. 1). This partitioning of anesthetic may explain the difference in degree of symptoms. Patients experiencing profound sensory and motor block obviously would have had more anesthetic deposited in the subdural space.

Another explanation regarding the difference in symptomatology may relate in part to the anatomic distribution of sensory, sympathetic, and motor nerve fibers. The anterior nerve roots carry motor and sympathetic nerve fibers, while sensory fibers are within posterior nerve roots. Because the subdural space has more potential capacity posteriorly and laterally, one should expect a sensory block. Meanwhile, a motor or sympathetic block would be present only if local anesthetic traveled anteriorly within this

subdural space (Fig. 2). Therefore, positioning of the patient after the block would influence the type of block to a large extent. Moreover, a motor and sympathetic block would occur more readily if a patient were in the lateral position, whereas sensory block would predominate if the patient were supine after the injection.

The absence of significant hypotension, in conjunction with a profound motor block as demonstrated by some of our patients, may reflect hydration status more than anything else. The hypotension seen in our patients was dramatic in certain cases, but was easily treated in all cases with relatively small amounts of fluid (250–500 cc) and small doses of ephedrine. Only one patient required 15 mg ephedrine. All others with hypotension responded to 5 or 10 mg ephedrine. Hypotension, which is easily treated, has been a feature of all previously confirmed subdural injections (16). This contrasts accidental subarachnoid injection where hypotension is characteristically more profound and difficult to correct.

The cadaveric dissection was performed to further exemplify the presence and anatomic proportion of the subdural space. It is well accepted that the subdural space exists in the cerebral meninges, and that certain clinical entities are seen when pathology is present in the subdural space (e.g., subdural hematoma). However, the extension of the subdural space down into the spinal segment of the meninges has been previously regarded by some authors as having questionable clinical significance (4). Our dissection supports the presence of the subdural space within

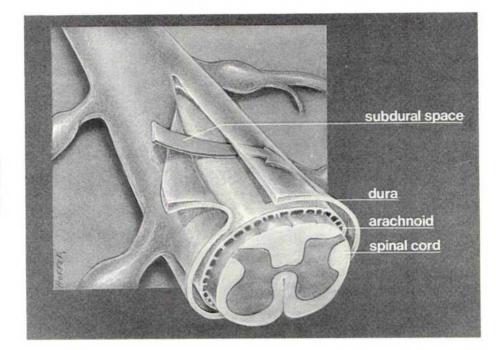


Figure 2. This illustration shows the anatomic relationship of dura and arachnoid. The subdural space exists as a potential space encircling the arachnoid membrane and contained within the dura.

the spinal cord segment of the meninges. A previous study on autopsy subjects has also portrayed the subdural space as a readily identifiable potential space. In our dissection, the potential subdural space and its relationship to the dura and arachnoid membranes was found to be similar to its portrayal by other authors (4,11,13). As depicted in Figure 1, a needle may pierce the dura but not the arachnoid and be contained within the subdural space. Local anesthetics, if deposited here, can travel cephalad and caudad in this narrow potential space, producing the unexpected extensive sensory, sympathetic, and motor blocks encountered in this series of therapeutic epidural drug depositions.

In conclusion, after subdural deposition of a local anesthetic, the development of an extensive sensory and motor block, with or without hypotension, may occur up to 30 minutes after the injection. The differential diagnosis of a possible subdural injection should be entertained as readily as one would suspect a subarachnoid injection. A subdural block should be considered when there has been extensive sensory or motor blockade after a negative CSF aspiration test when small volumes and dilute concentrations of local anesthetics are utilized. We recommend that outpatients receiving epidural injections of any amount of local anesthetics be observed for at least 1 hour before discharge because of potential for a subdural injection.

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Oral Atropine Premedication in Infants Attenuates Cardiovascular Depression during Halothane Anesthesia

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MILLER BR, FRIESEN RH. Oral atropine premedication in infants attenuates cardiovascular depression during halothane anesthesia. Anesth Analg 1988;67:180–5.

The efficacy of oral atropine premedication in attenuation of the cardiovascular depression associated with halothane anesthesia has not been previously evaluated. A solution containing either oral atropine 0.04 mg/kg (HI), 0.02 mg/kg (LO), or a placebo (NO) was randomly administered to 36 infants 1–6 months old and 36 infants 7–15 months old 30–90 minutes before induction of anesthesia. The onset of action of atropine was approximately 25 minutes after administration as determined by a 15% increase in heart rate (HR) above baseline levels. Heart rate, systolic blood pressure (SBP), and mean arterial blood pressure (MAP) were then measured at 1-minute intervals starting just

before induction of anesthesia and continuing until onset of surgical stimulation during anesthesia with halothane (up to 3%), nitrous oxide (60%), and oxygen (40%). In infants 1–6 months old, either dosage of oral atropine preserved HR and SBP as compared with placebo. In infants 7–15 months old, either dosage preserved HR but not SBP. The severity of hypotension was greatest in infants 1–6 months of age given placebos. No significant differences existed between oral atropine 0.04 mg/kg or 0.02 mg/kg in either age range. It is concluded that premedication with oral atropine 0.02 mg/kg is effective in attenuating the cardiovascular depression associated with halothane anesthesia in infants.

Key Words: PARASYMPATHETIC NERVOUS SYSTEM—atropine. PREMEDICATION—atropine.

Inhalation of halothane, nitrous oxide, and oxygen is the most common method of inducing general anesthesia in pediatric patients (1,2). Halothane directly depresses myocardial function in a dose-related fashion in infants as demonstrated by echocardiographic and pulse Doppler cardiac output studies (3–5). Premedication with IM atropine in patients 1–6 months of age can attenuate the cardiovascular depression associated with halothane (6). However, intramuscular administration results in patient discomfort and parental anxiety, with the risk of hematoma or sterile abscess formation and nerve damage.

Oral atropine has frequently been used in combination with other premedicants and is an effective antisialogogue (7–9), but its efficacy in attenuating cardiovascular depression in infants anesthetized with halothane has not been evaluated. The purpose of this prospective, blinded, randomized study was to evaluate the efficacy of oral atropine premedication in infants of various ages.

Methods

The study was approved by the Institutional Review Board at our institution and informed parental consent was obtained for each infant. Seventy-two infants scheduled for elective surgical procedures were studied. All were between 1-15 months of age, >44 weeks conceptual age, ASA I or II, without known cardiac or pulmonary disease, and had been fasting for a minimum of 4 hours. Premature infants and full-term neonates were excluded from this study because of the known immaturity of the mammalian fetal and neonatal cardiovascular systems (10) and the decreased minimum alveolar concentration requirements for halothane and isoflurane (11,12). The patients were separated into two age groups, 1-6 months and 7-15 months, with 36 patients in each age group. Using a table of random numbers, they were then placed into three premedication groups: 12 patients in each age group received oral atropine 0.04 mg/kg (HI); 12 patients in each age group received oral atropine 0.02 mg/kg (LO); and 12 patients in each age group received a placebo (NO). No other medications were administered.

The oral atropine premedication was prepared by the pharmacy using atropine in a concentration of 0.4

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mg/ml contained in a 20-ml vial (a total of 8.0 mg of atropine) mixed with 80 ml of simple syrup, to yield a final volume of 100 ml and concentration of 0.08 mg/ml. The HI group received 0.5 ml/kg (0.04 mg/kg) and the LO group received 0.25 ml/kg (0.02 mg/kg), with the NO group receiving only the simple syrup in a volume of 0.25 ml/kg. The medication, refrigerated and arbitrarily given a 4-week expiration date from the time of preparation, was replaced three times during the study. Medication was administered 30–90 minutes before induction of anesthesia by one of us (BRM), and the anesthesia care team was unaware of the type of solution the patients received.

Before administering the premedication, a baseline measurement of heart rate (HR), systolic blood pressure (SBP), and mean arterial pressure (MAP) was attempted using a Dinamap 847 monitor and 950 recorder (Critikon, Tampa, FL). If the infant would not tolerate the procedure, baseline measurements were not obtained. In the group that tolerated the blood pressure cuff, serial measurements of HR, SBP, and MAP were made and recorded at 5-minute intervals from premedication until transport to the operating room. Measurements during this time were used to determine the onset of action of oral atropine. This was defined as the time from premedication until the development of a sustained HR >15% above baseline levels.

In the operating room noninvasive monitors were applied and preinduction levels of HR, SBP, and MAP were measured using the same Dinamap monitor and recorder. Further measurements were made at 1-minute intervals starting immediately before induction of anesthesia and continuing until onset of surgical stimulation (i.e. incision, injection of local anesthetic, or examination). Anesthesia was induced using halothane in increasing inspired concentrations up to 3% in a mixture of 60% N₂O and 40% O₂ at a flow rate of 5 L/min using a semiclosed circle system with assisted ventilation. Immediately after induction, an intravenous catheter was inserted and 6-20 ml/kg of a solution of dextrose 5% in lactated Ringer's was infused before surgical stimulation. Tracheal intubation was performed under deep halothane (3%) anesthesia defined as a decrease in respiratory effort, pupils in the midline and constricted, and an absence of abdominal muscular tone. After intubation, the inspired halothane concentration was decreased to 1.25% and maintained until surgical stimulation, at which time data collection ceased.

Intravenous atropine was administered any time between induction and surgical stimulation if the HR was <100 beats/min or the percentage decrease in

SBP was >50% (SBP $\Delta > 50\%$) below preinduction values. If intravenous atropine was administered, data collection ceased except for determining the time from induction to surgical stimulation.

In each premedication group the following were recorded: age, weight, duration of fasting, time between administration of medication until induction of anesthesia, baseline and preinduction measurements of HR, SBP, and MAP, volume of IV fluids infused before surgical stimulation, lowest values of HR, SBP, and MAP measured during the time between induction of anesthesia and surgical stimulation, duration of time between induction of anesthesia and surgical stimulation, and the incidence of significant bradycardia and hypotension requiring administration of IV atropine. Side effects of oral atropine, such as flushing and increased irritability were recorded preand postoperatively. Problems arising from frequent blood pressure measurements were also recorded. The antisialogogue effect of the oral atropine dosages was graded by the laryngoscopist based on whether the upper airway was either dry, moist, or wet using a numerical rating score of 2, 1, or 0, respectively.

The data were analyzed by analysis of variance (ANOVA) in the three premedication groups. Intergroup comparisons were made using the Scheffe F-Test. The NO groups in the two age ranges were compared with each other using a two-tailed unpaired Student's t-test to evaluate the effects of halothane anesthesia on SBP. Chi-square analysis was used to compare the incidence of HR < 100 beats/min and SBP $\Delta > 50\%$ in the oral atropine groups (HI and LO) versus placebo. Statistical significance was assumed when P < 0.05.

Results

There were no significant differences between the HI, LO, or NO groups in age, weight, duration of fasting, IV fluids infused, time between administration of the premedication and induction of anesthesia, and time between induction and surgical stimulation (Tables 1 and 2). Some baseline HR, SBP, and MAP measurements were difficult to obtain because of patient movement and crying. Baseline measurements were, however, obtained in 21 of 36 patients aged 1–6 months and in 18 of 36 patients aged 7–15 months. There were no significant differences among the groups in baseline HR, SBP, or MAP values in either age range (Tables 1 and 2).

Only 28 infants tolerated serial preoperative measurements well enough to allow determination of time of onset of action of atropine. Onset of action

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Table 1. Patient Characteristics in the 1-6 Month Age Range

	HI (0.04 mg/kg)	LO (0.02 mg/kg)	NO (placebo)	P†
Age (mo)	3.5 ± 1.8	3.0 ± 1.5	3.7 ± 1.8	>0.5
Weight (kg)	5.9 ± 1.5	5.6 ± 1.3	6.2 ± 1.3	>0.6
NPO (hr)	6.4 ± 2.2	6.1 ± 2.7	7.2 ± 3.0	>0.6
IV Fluids (ml/kg)	12.2 ± 4.5	11.0 ± 2.3	12.8 ± 3.2	>0.4
Baseline HR (beats/min)*	164.2 ± 35.3	149.1 ± 17.3	161.4 ± 22.3	>0.4
Baseline SBP (mm Hg)*	103.0 ± 3.6	95.9 ± 18.8	97.6 ± 22.5	>0.7
Baseline MAP (mm Hg)*	84.0 ± 11.6	79.3 ± 18.2	72.4 ± 28.3	>0.6
Time (min) from				
Premedication-induction	53.6 ± 17.3	61.0 ± 16.0	51.0 ± 23.6	>0.4
Induction-incision	17.8 ± 5.1	18.8 ± 3.2	15.6 ± 5.1	>0.3

Values are expressed as mean \pm sp; n = 12 in each group.

Table 2. Patient Characteristics in the 7–15 Month Age Range

	HI (0.04 mg/kg)	LO (0.02 mg/kg)	NO (placebo)	P†
Age (mo)	10.5 ± 2.1	10.1 ± 2.4	9.1 ± 1.5	>0.25
Weight (kg)	8.9 ± 1.2	8.9 ± 1.0	8.5 ± 1.1	>0.6
NPO (hr)	9.6 ± 3.1	9.5 ± 2.9	9.1 ± 3.6	>0.9
IV Fluids (ml/kg)	10.3 ± 1.1	9.6 ± 1.3	10.8 ± 2.9	>0.29
Baseline HR (beats/min)*	133.5 ± 13.7	134.0 ± 14.2	131.5 ± 21.4	>0.97
Baseline SBP (mm Hg)*	107.4 ± 13.4	101.3 ± 8.7	90.8 ± 7.9	>0.08
Baseline MAP (mm Hg)*	83.8 ± 6.8	84.7 ± 11.3	73.5 ± 7.0	>0.12
Time (min) from				
Premedication-induction	60.3 ± 17.1	48.9 ± 12.9	51.3 ± 16.3	>0.19
Induction-incision	17.3 ± 5.4	17.3 ± 9.0	15.3 ± 2.5	>0.67

Values are expressed as mean \pm sp; n = 12 in each group.

Abbreviations as in Table 1

†Analysis of Variance.

was 24.6 \pm 9.8 minutes (range 13–39) in the HI group and 21.3 \pm 5.5 minutes (range 14-26) in the LO group. There was no sustained increase in HR in the NO group.

In patients 1–6 months of age, both HI and LO doses of oral atropine significantly attenuated the depression of HR, SBP, and MAP during halothane anesthesia (Table 3). In patients 7–15 months of age, oral atropine significantly attenuated depression of HR, but did not alter depression of SBP and MAP when compared with placebo (Table 4). There were no significant differences between the HI and LO groups regarding preservation of HR, SBP, and MAP in either age range. The time from induction to lowest levels of HR and SBP was significantly greater in patients 1-6 months of age who were premedicated with oral atropine. This time was not affected by atropine in patients 7-15 months of age.

In the placebo groups, the decrease in SBP in 1-6-month-old patients was significantly greater than in the 7-15-month-old patients, as was the percentage decrease in SBP, although preinduction SBP was not significantly different in the two age ranges.

Significantly fewer patients given oral atropine in both age ranges required IV atropine administration for treatment of low HR when compared with the NO group. Significantly fewer infants 1-6 months of age required IV atropine for treatment of low SBP than did those in the placebo group. However, in the patients 7–15 months of age, there was no significant difference between oral atropine and placebo in the frequency of the use of atropine for treatment of low SBP (Table 5).

The antisialogogue effect (Mean ± sp) in the 1-6month-old age range was significantly greater in the HI (1.75 \pm 0.5) and LO (1.42 \pm 0.5) groups than in the NO (0.25 ± 0.5) group with no significant difference between the HI and LO groups. In the 7-15-monthold range the antisialogogue effect was significantly greater in the HI (1.50 \pm 0.5) than in the LO (0.92 \pm

Abbreviations: NPO, nil per os, HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure. *HI group, n = 6; LO group, n = 10; NO group, n = 5.

^{*}HI group, n = 8; LO group, n = 6; NO group, n = 4.

<u>Table 3</u>. Age Range 1–6 Months: Changes in Heart Rate, Systolic Blood Pressure, and Mean Arterial Pressure during Halothane Anesthesia after Oral Atropine Premedication

	HI (0.04 mg/kg)	LO (0.02 mg/kg)	NO (placebo)	p*
Heart rate	0.00	88/	ivo (placebo)	1
Preinduction beats/min	196.3 ± 14.1	181.4 ± 20.0	170.6 ± 31.5	< 0.033
Lowest (beats/min)	155.7 ± 12.5	154.2 ± 9.6	103.4 ± 18.6	< 0.0001
Percent change (%)	-21.3 ± 6.5	-14.5 ± 9.7	-37.8 ± 12.5	< 0.0001
Systolic blood pressure	21.5	41.3 - 2.7	-37.6 ± 12.3	<0.0001
Preinduction (mm Hg)	98.3 ± 15.4	101.5 ± 16.7	104.4 ± 17.4	>0.67
Lowest (mm Hg)	68.3 ± 17.7	66.7 ± 14.5	52.3 ± 10.9	< 0.021
Percent change (%)	-30.8 ± 17.4	-34.3 ± 14.7	-48.2 ± 11.0	< 0.015
Mean arterial pressure		=	40.2 = 11.0	0.015
Preinduction (mm Hg)	76.4 ± 13.5	86.5 ± 13.7	86.9 ± 20.6	>0.2
Lowest (mm Hg)	52.4 ± 13.9	52.7 ± 12.2	40.7 ± 10.0	<0.03
Percent change (%)	-32.0 ± 15.3	-37.8 ± 15.1	-52.1 ± 15.0	< 0.008
Induction (min) to		57.0 - 15.1	52.1 = 15.0	~0.000
Lowest HR	8.3 ± 5.5	5.4 ± 2.8	4.2 ± 2.0	< 0.034
Lowest SBP	9.8 ± 5.7	12.0 ± 6.8	5.5 ± 2.4	< 0.016

Values are expressed as mean \pm sp; n = 12 in each group.

Table 4. Age Range 7–15 Months: Changes in Heart Rate, Systolic Blood Pressure, and Mean Arterial Pressure during

	HI (0.04	LO (0.02		
	mg/kg)	mg/kg)	NO (Placebo)	P*
Heart Rate				
Preinduction beats/min	172.6 ± 23.5	168.3 ± 22.2	169.9 ± 24.7	>0.9
Lowest (beats/min)	142.3 ± 17.5	125.3 ± 20.1	94.4 ± 9.8	< 0.0001
Percent change (%)	-18.0 ± 7.6	-25.0 ± 12.3	-43.1 ± 11.5	< 0.0001
Systolic blood pressure			1011 = 1110	<0.0001
Preinduction (mm Hg)	108.8 ± 13.6	108.6 ± 13.5	111.3 ± 15.0	>0.87
Lowest (mm Hg)	74.8 ± 26.4	81.5 ± 12.6	68.9 ± 13.6	>0.37
Percent change (%)	-36.6 ± 18.9	-27.9 ± 9.2	-37.3 ± 14.4	>0.26
Mean arterial pressure				-0.20
Preinduction (mm Hg)	90.7 ± 15.8	94.8 ± 16.6	93.9 ± 15.9	>0.81
Lowest (mm Hg)	59.4 ± 20.7	62.1 ± 11.4	51.7 ± 9.9	>0.31
Percent change (%)	-39.9 ± 16.0	-37.4 ± 11.8	-44.1 ± 11.8	>0.49
Induction (min) to			1111 - 1110	-0.49
Lowest HR	8.3 ± 6.9	4.3 ± 1.6	5.3 ± 2.6	>0.08
Lowest SBP	8.5 ± 4.6	7.4 ± 5.9	5.4 ± 2.7	>0.00

Values are expressed as mean \pm sp; n = 12 in each group.

0.7) group with both significantly greater than the NO (0.17 \pm 0.4) group.

The only notable side effect of oral atropine was flushing in four patients (three HI and one LO) in the 1–6 month age range, which resolved in less than 4 hours. Hyperthermia or irritability were not observed in any patient. Problems observed in association with BP measurement included arm petechiae distal to the cuff in four patients and chest wall irritation after arm movement while the cuff was applied in two awake patients.

Discussion

These data demonstrate that premedication with oral atropine 0.02 mg/kg or 0.04 mg/kg is effective in attenuating the cardiovascular depressant effects of halothane in infants. In infants 1–6 months of age, both the severity and the incidence of bradycardia and hypotension were decreased by oral atropine premedication (Tables 3 and 5). In patients 7–15 months of age, oral atropine premedication decreased the severity and incidence of HR depression

Abbreviations as in Table 1. *Analysis of Variance.

Abbreviations as in Table 1. *Analysis of variance.

<u>Table 5</u>. Incidence of Significant Bradycardia and Hypotension in Infants during Halothane Anesthesia after Oral Atropine Premedication

	A	ge range 1–6 monti	hs	Age range 7–15 months		
	Oral atropine*	Placebo†	X ²	Oral atropine*	Placebot	χ^2
HR < 100 beats/min	0	7	P < 0.01	3	9	P < 0.01
$SBP\Delta > 50\%$	2	6	P < 0.01	3	2	P > 0.8
Either	2	10	P < 0.01	5	9	P < 0.01

Abbreviations: SBPΔ, decrease in systolic blood pressure; other abbreviations as in Table 1.

*Oral atropine group, n = 24. †Placebo group, n = 12.

but did not significantly affect changes in SBP or MAP (Tables 4 and 5). Infants 7–15 months of age had SBP depression of less severity and frequency than did infants 1–6 months old.

Clinically evident cardiovascular depression during halothane anesthesia in infants 1-6 months old has been well described (6,11,13,14). The concept that sensitivity to the cardiovascular depressant effects of halothane is inversely related to age is supported by laboratory research (15-17). Rao et al. (15) exposed neonatal and adult isolated rat atrial preparations to halothane and demonstrated a dose-dependent depression of isometric contraction. The adult atria required nearly twice the halothane concentration as that of the neonatal atria to achieve the same amount of depression. Cook et al. (16) found the myocardial concentration of halothane in 15-day-old rats at the point of cardiovascular failure to be less than that in 30- or 60 day-old-rats, despite the increased anesthetic requirement for halothane in the younger rats. Wear et al. (17) demonstrated that at equipotent concentrations of halothane, neonatal rabbits developed hypotension more often than did adult rabbits. These age-related differences are probably explained by the fact that the mammalian heart is immature at birth and continues to develop postnatally for some

Comparison of the placebo groups in the two age ranges in the present study also lends support to the concept that sensitivity to the cardiovascular depressant effects of halothane is age-related. At the same inspired halothane concentration, infants 1–6 months of age experienced greater and more frequent decreases in SBP than did infants 7–15 months of age (Tables 3–5).

Because the ventricles of the young infant's heart are so noncompliant (10), cardiac output is highly dependent on HR. Atropine administration supports cardiac output by increasing HR. Blood pressure depends on both cardiac output and systemic vascular resistance. If systemic vascular resistance changes very little in the young infant receiving halothane, as

<u>Table 6</u>. Comparison of Patient Characteristics and Attenuation of Cardiovascular Depression in Infants 1–6 Months Old Receiving either Oral Atropine or Intramuscular Atropine Premedication

	Oral atropine*	Intramuscular atropine†
Age (mo)	3.2 ± 1.7	3.2 ± 1.8
Weight (kg)	5.8 ± 1.4	5.5 ± 1.3
NPO (hr)	6.3 ± 2.4	6.2 ± 1.7
Heart rate		
Preinduction (beats/min)	188.9 ± 18.5	198.0 ± 18.0
Lowest (beats/min)	154.9 ± 10.9	162.0 ± 14.0
Percent change (%)	-17.9 ± 8.8	-18.0 ± 8.0
Systolic blood pressure		
Preinduction (mm Hg)	99.9 ± 15.8	98.0 ± 14.0
Lowest (mm Hg)	67.5 ± 15.9	65.0 ± 14.0
Percent change (%)	-32.6 ± 15.9	-34.0 ± 15.0
Mean arterial pressure		
Preinduction (mm Hg)	81.5 ± 14.3	85.0 ± 14.0
Lowest (mm Hg)	52.5 ± 12.8	48.0 ± 11.0
Percent change (%)	-34.9 ± 15.1	-44.0 ± 10.0

Values are expressed as mean ± sp.

Abbreviations as in Table 1

†Intramuscular atropine 0.02 mg/kg (Reference 6); n = 30.

the piglet study of Boudreaux et al. (18) suggests, then blood pressure is highly dependent on cardiac output. Thus, atropine supports blood pressure by maintaining cardiac output.

Intramuscular atropine 0.02 mg/kg has been shown to attenuate cardiovascular depression during halothane administration to infants 1–6 months of age (6). The present study indicates that oral atropine provides comparable cardiovascular protection to similar patients during similar halothane anesthesia (Table 6).

The oral route of administration was readily accepted by both patients (only one infant spit out a portion of the solution and was excluded from the study) and by their parents. The onset of action of about 25 minutes is satisfactory for elective use. Flushed skin in four patients was the only noted side effect of oral atropine; this was transient and can

^{*}Oral atropine group is the combined HI and LO groups in the 1–6 month age range; n=24.

probably be minimized by using 0.02 mg/kg instead of 0.04 mg/kg. The only significant difference that we observed between the two doses was that 0.04 mg/kg was a more effective antisialogogue than 0.02 mg/kg, although the lower dose was still significantly better than placebo. The solution is inexpensive and easily prepared.

We conclude that premedication with oral atropine 0.02 mg/kg is effective in attenuating the cardiovascular depressant effects of halothane anesthesia in infants.

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Clinical Reports

Monitoring of Arterial Hemoglobin Oxygen Saturation Using a Tongue Sensor

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Key Words: MEASUREMENT TECHNIQUES—pulse oximetry. ANESTHESIA—pediatric.

The ability to monitor continuous arterial hemoglobin oxygen saturation noninvasively using a sensor placed on a hand, finger, or toe allows prompt recognition and treatment of desaturation in a variety of clinical settings (1,2). Pediatric patients in general and specifically those with congenital heart disease are unique in their potential to change arterial oxygen saturation acutely. These patients, who not uncommonly have minimal cardiopulmonary reserve, benefit from early detection of such changes using pulse oximetry. Unfortunately, our experience indicates that pulse oximetry does not function reliably in the operating room environment in two groups of children: 1) infants, and 2) patients undergoing hypothermic cardiopulmonary bypass with circulatory arrest for cardiac surgery. Peripheral vasoconstriction with decreased pulse amplitude in the currently used sensor sites (fingers and toes) is the primary reason for failing to consistently obtain a reliable saturation. We sought a sensor site that would be more reliable under these conditions, i.e., hypothermia, decreased cardiac output, and increased systemic vascular resistance. The following cases are examples of use of a more central site, the tongue.

Case Reports

Case 1

A 50-kg 15-year-old boy with complete AV canal and tetralogy of Fallot was scheduled for complete repair using hypothermic cardiopulmonary bypass and circulatory arrest. Before induction of anesthesia, a sensor (Nellcor Oxisensor, N25) was placed on the patient's left thumb. After induction, tracheal intubation and placement of vascular catheters the patient's rectal temperature had fallen to 35.5°C. The finger sensor that had been functioning normally was now functioning only intermittently. An infant digit oxygen transducer (Nellcor Oxisensor, I-20) was modified for application on the patient's tongue (Fig. 1). The sensor was shortened so that an equal amount of adhesive was present on each side of the two optical components. The aluminum nasal bridge of an operating room mask was then cut to the size of the shortened sensor (Fig. 2). The additional tape provided with the sensor was wrapped around the aluminum to adhere the sensor to the aluminum strip, making certain that the transparent windows were not covered (Fig. 3). The aluminum was then bent in a configuration such that the transparent windows directly opposed each other (Fig. 4). The patient's tongue was gently pulled forward, dried, and the sensor applied longitudinally on the tongue. The tongue was then repositioned in the mouth and the sensor cable taped to the face. Before initiation of cardiopulmonary bypass the saturations from the tongue probe correlated with the saturations calculated from arterial blood samples. It was noted that signal interference from the electrocautery unit was markedly less using the tongue instead of a peripheral site. On termination of bypass at a rectal temperature of 33.5°C, the tongue sensor functioned imme-

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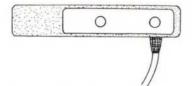
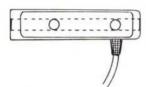


Figure 1. Nellcor I-20 pulse oximeter sensor.



<u>Figure 2</u>. Shortened Nellcor I-20 sensor placed on a narrow piece of aluminum cut to the size of the shortened sensor.

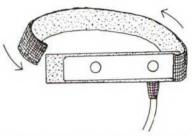
diately. The finger sensor began to function 10–15 minutes after bypass but only intermittently for the duration of the postbypass period. An arterial blood sample taken from an indwelling catheter in the right radial artery showed an oxygen saturation of 94% (Po_2 , 68 mm Hg) when the tongue showed a saturation of 94% and the finger sensor was not functioning. Examination of the finger showed no change in sensor position and the probe functioned adequately when subsequently applied to another individual.

Case 2

A 2.0-kg 3-week-old premature infant was scheduled for ligation of a patent ductus arteriosus. Both a left toe and tongue sensor were applied before placing the patient in the left lateral position. The tongue probe was less affected by electrocautery and by motion in the surgical field. At the end of the procedure, despite attempts to keep the infant warm, the rectal temperature was 35.2°C. The tongue sensor continued to function continuously and the toe sensor only intermittently. Examination of the toe sensor showed no change in position and it also functioned normally when placed on another individual.

Case 3

A 3.8-kg 11-week-old infant with agenesis of the right lung, tracheal stenosis, and small airways disease was undergoing bronchoscopy and tracheal dilation through a tracheostomy stoma. A sensor was placed on the child's left foot and was functioning until a perforation of the distal trachea with the rigid bron-



<u>Figure 3</u>. Piece of adhesive from the I-20 package used to keep sensor on aluminum strip.



<u>Figure 4</u>. The aluminum strip is carefully bent to ensure that the optical windows are directly across from each other when the sensor is placed on the tongue.

choscopy occurred. Diminished breath sounds were noted in the left chest, the child's skin became pale and mottled indicating marked cutaneous vasoconstriction, followed shortly by bradycardia. The foot sensor ceased functioning. A modified sensor was immediately placed on the child's tongue. The sensor began to read immediately (oxygen saturation, 53%). The child's position, position of the bronchoscope, and ventilatory pattern were guided by the saturations indicated by the tongue sensor. After resuscitation and establishing what was believed to be an acceptable ventilatory pattern the tongue sensor saturation reading was 83-86% and an arterial blood sample showed a Po2 of 57 mm Hg. Emergency cardiopulmonary bypass was instituted with hypothermic arrest to repair the trachea. At the termination of bypass the tongue sensor again provided information useful in guiding the ventilation. The peripheral sensor did not function. Both sensors were observed at the end of the case; the foot probe was securely positioned as initially placed.

Discussion

Our observations and those of others that peripheral sensors do not function reliably under conditions of hypothermia and grossly abnormal systemic vascular resistance made us seek an alternative sensor location that would provide more reliable and continuous assessment of arterial hemoglobin oxygen saturation during such conditions (3). We thought that the arterial pulsations in the tongue would be less influenced by intraoperative conditions. The observations in these three patients where the tongue was used to monitor arterial oxygen saturation support this belief. In addition the relatively protected intraoral site is less influenced by motion of the surgical team than is a peripheral site. Protection from electrosurgical interference may be in part explained by the fact that the mouth functions as a Faraday shield when the tongue and sensor are placed well inside the oral cavity. However, positive pressure ventilation results in more profound variation in the signal amplitude from the tongue sensor than from other more peripheral sites and the changes in amplitude appeared to be augmented during hypovolemia. The resultant saturations, however, continued to correlate with

arterial blood gas samples although heart rate was not accurate. Monitoring arterial oxygen saturation via a non-invasive tongue sensor shows promise for application in cardiac surgery and in other settings where conventional sites prove unreliable. Design modification and systematic evaluations have been initiated.

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One-Lung Ventilation of the Newborn with Tracheoesophageal Fistula

Anis Baraka, MD, Samir Akel, MD, Sanie Haroun, MD, and Alex Yazigi, MD

Key Words: ANESTHESIA—pediatric. GASTROINTESTINAL TRACT—esophageal fistula.

Intermittent positive pressure ventilation (IPPV) of the newborn having esophageal atresia associated with distal tracheoesophageal fistula (TEF) may result in marked distention of the gastrointestinal tract, which can be complicated with serious cardiovascular embarrassment (1).

The present report shows that, in two newborns having surgical repair of TEF, selective bronchial intubation can be safely used to achieve one-lung ventilation (OLV) while the sidewall of the tube serves to occlude the fistula, thereby retarding gas insufflation into the stomach.

Case Report 1

The newborn was a 3-day-old, 2.5-kg male, the product of a full-term pregnancy and normal vaginal delivery. The baby had excessive drooling of saliva and vomiting after attempted feeding. The patient was diagnosed as having esophageal atresia associated with distal TEF. X-ray film of the chest revealed bilateral pneumonia.

The baby was scheduled for preliminary gastrostomy. He was premedicated with IM atropine 0.1 mg, After awake tracheal intubation, anesthesia was achieved by spontaneous breathing of 50% N₂O:O₂ and 0.5–1% halothane. The baby developed apnea. Controlled ventilation produced gastric distention and bradycardia. Atropine 0.1 mg was injected intravenously and the tracheal tube was pushed down into the right main bronchus as evidenced by chest auscultation and X-ray film (Fig. 1). The heart rate

increased. One-lung ventilation (OLV) via the bronchial tube was not associated with gastric inflation, and was continued using halothane in 100% oxygen until gastrostomy was performed. After gastrostomy, the tracheal tube was withdrawn above the carina and two-lung ventilation was maintained (Fig. 2) until the baby resumed regular spontaneous breathing.

Case Report 2

A 2-week-old, 2.8-kg female, the product of a normal vaginal delivery, had esophageal atresia associated with distal TEF complicated with bilateral pneumonia. A preliminary gastrostomy was done under local anesthesia at the age of 1 week and antibiotic therapy was started. The pneumonia cleared after 1 week. The baby was then scheduled for right posterolateral thoracotomy and extrapleural repair of the TEF.

The baby was premedicated with IM atropine 0.1 mg. Awake orotracheal intubation was performed using a 3-mm internal diameter tracheal tube. Selective left bronchial intubation was achieved by turning the tube in the trachea through 180° before advancing it down into the left main bronchus (2). Chest auscultation confirmed selective left bronchial intubation. The tube was secured in position and ventilation was controlled using 1-2% halothane in 100% oxygen. After posterolateral thoracotomy, the TEF was repaired via the extrapleural approach. The fistula was divided and the tracheal end was sutured. An esophageal anastomosis was also performed. The surgical procedure was significantly facilitated by having the right lung on the operative side motionless and collapsed, while contralateral left bronchial intubation was used to provide OLV of the dependent left lung. Arterial blood gas analysis after 30 minutes of OLV showed Po₂ 80 mm Hg, Pco₂ 42 mm Hg, and pH 7.45.

After repair of the TEF, the tube was withdrawn from the left bronchus into the trachea above the suture line, to achieve two-lung ventilation and to

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Figure 1. Chest X-ray film during OLV after right bronchial intubation.

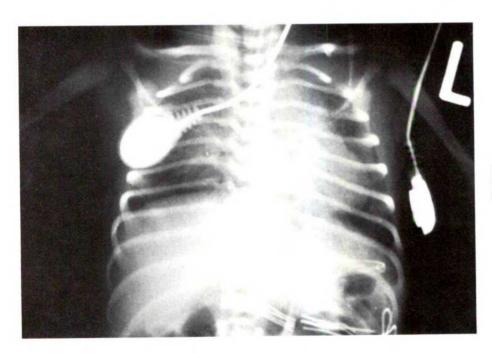


Figure 2. Chest X-ray film during TLV after withdrawal of the tracheal tube above the carina.

assure that closure of the TEF was airtight. At the end of surgery, halothane anesthesia was discontinued, and the baby was extubated after resuming adequate spontaneous breathing. Arterial blood gas analysis while the baby was breathing 100% oxygen by face mask revealed Po₂ 160 mm Hg, Pco₂ 30 mm Hg, and pH 7.46. Blood gas tensions while breathing room air were Po₂ 77 mm Hg, Pco₂ 40 mm Hg, and pH 7.46. Postoperative chest X-ray films showed expansion of both lungs with no evidence of atelectasis or pneumothorax.

Discussion

Intermittent positive pressure ventilation of the newborn with esophageal atresia associated with distal TEF can result in marked distention of the gastrointestinal tract that may be severe enough to be associated with gastric rupture (3), or serious cardiovascular embarrassment (1). Gastric distention during IPPV will be exaggerated whenever the lungs of the newborn are noncompliant (4) secondary to pneumonia, RDS, or the unusual combination of TEF and diaphragmatic hernia (5). An initial gastrostomy under local analgesia may decrease gastric inflation and aspiration pneumonia (1). However, gastrostomy may compound the ventilatory problem during IPPV in the presence of noncompliant lungs by creating a low-pressure vent (4). A solution to this problem has been devised by Filston et al. (4) who used a bronchoscope to place a Fogarty catheter into the TEF and inflated the balloon to occlude the fistula. However, both gastrostomy and bronchoscopic occlusion of the fistula are time-consuming and cannot be rapidly applied in emergency situations.

Salem et al. (6) suggested occlusion of the TEF by placing the tip of the tracheal tube between the carina and the TEF; both lungs can then be ventilated without insufflating gases through the fistula. However, to ensure effective blocking of the fistula, the tracheal tube should not have a side hole and the tube should be positioned with its bevel facing anteriorly. Also, the fistula is usually located just proximal to the carina, which makes it difficult to secure the tube in a position between the carina and the TEF. Any slight upward movement of the tube may bring its bevel above the TEF or even into the TEF itself. We found it more practical in the first baby, who developed gastric distention and bradycardia secondary to IPPV, to advance an ordinary tracheal tube down to the right main bronchus where it could be easily secured in position. Because of the anatomy of the tracheobronchial tree in infants and children (7), right bronchial intubation can be easily performed (8) in emergency situations; one-lung ventilation (OLV) is achieved while the sidewall of the tube serves to occlude the TEF, thereby avoiding gas insufflation into the stomach.

The technique of selective bronchial intubation was used electively in the second newborn to provide OLV during the definitive repair of TEF. Because a right thoracotomy was used, contralateral left bronchial ventilation was performed to provide OLV of the dependent left lung and to allow a motionless collapsed right lung on the operative side. Arterial blood gas tensions during OLV showed adequate Po₂ and Pco₂ levels. The technique markedly facilitated the extrapleural approach for surgical repair of the

TEF and decreased the possibility of accidental pleural injury during the surgical procedure.

In conclusion, the present report shows that in the newborn with esophageal atresia associated with distal TEF, IPPV may result in marked gastric distention complicated with cardiovascular embarrassment. Selective bronchial intubation can provide OLV while the sidewall of the tube serves to occlude the TEF, thereby avoiding gas insufflation into the stomach. Right bronchial intubation was performed in our first newborn undergoing preliminary gastrostomy, whereas left bronchial intubation was used in our second newborn undergoing right thoracotomy for the definitive repair of TEF. Checking arterial blood gas during OLV of the second newborn revealed adequate Po₂ and Pco₂ levels.

OLV is potentially hazardous because it creates a major right-to-left intrapulmonary shunt. Spotchecking of blood gas during prolonged OLV may miss periods of clinically important hypoxemia. That is why continous monitoring of oxygenation by a pulse oximeter is advised when this technique is used.

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Early Detection of Patent Foramen Ovale By Two-Dimensional Contrast Echocardiography for Prevention of Paradoxical Air Embolism During Sitting Position

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Key Words: HEART—congenital defects. EMBOLISM—air. MEASUREMENT TECHNIQUES—echocardiography.

The reports of paradoxical air embolism (PAE) during venous air embolism (VAE) in patients operated on n the sitting position (SP) are for the most part individual case reports, suggesting that the incidence ⊃f significant complications from PAE are relatively rate (1). Nevertheless these complications are serious and can be responsible for devastating neurologic consequences and air emboli to the coronary circulation (2). The passage of embolized air from right to left circulation generally occurs through a patent foramen ovale (PFO). Paradoxical air embolism has been demonstrated during anesthesia using transesophag∈al echocardiography (2-D TEE) (3). New developments in the ability to identify preoperatively patients with PFO may further decrease the mortality and the morbidity associated with episodes of PAE occurring in the SP.

This study reports the preoperative frequency of detected PFO by two-dimensional contrast echocardiography (2-D CE) in patients scheduled for a surgery in the SP and the incidence of intraoperative cardiac ischemia and postoperative clinical neurologic deficit observed in patients without detected PFO operated in the SP.

Methods and Materials

This prospective study was carried out over a 2-year period. Two hundred eighteen patients (68 women and 150 men) scheduled for a neurosurgical proce-

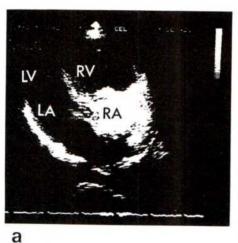
dure in the sitting position were studied. All patients gave their informed consent and institutional approval by the Ethics Committee was obtained. The mean age (±sD) of the patients who were scheduled to undergo cervical laminectomy (74 patients) or posterior fossa exploration (144 patients) was 45 ± 16 years. At least twenty-four hours before surgery a trained echocardiographer in an echo suite detected PFO by a preoperative 2-D CE performed in SP. Ten ml agitated sterile saline solution was injected through an 18-gauge catheter placed in an antecubital vein. The saline solution was prepared immediately before injection by vigorously shaking a vial containing the saline solution and then filling a syringe, carefully extruding all macroscopic air. Injection was accomplished by rapid manual compression of the syringe over a period of 2 to 3 seconds. Between four and eight injections were given in each patient to obtain optimal contrast effect. The 2-D echoes were recorded in the apical four-chamber view. Injections were performed during normal quiet respiration, during coughing, and at the time of release of the strain phase of the Valsalva maneuver. The presence of right-to-left shunting was established by observing transient echo targets cross from the right atrium to the left atrium or the left ventricle (Fig. 1).

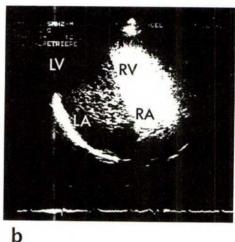
If a right-to-left shunt was demonstrated, SP was considered contraindicated and the surgery was performed in ventral or lateral position; only patients without identified right-to-left shunting underwent surgery in the SP. In these patients, induction of anesthesia consisted of thiopental (5 mg/kg) and fentanyl (5 μ g/kg) followed by vecuronium (8 mg) for intubation. A continuous infusion of fentanyl (0.05–0.1 μ g·kg⁻¹·min⁻¹) and 60% N₂O in O₂ during mechanical ventilation without positive end-expiratory pressure (PEEP) were used to maintain anesthesia. Intravascular volume loading with a dextran solution (10–15 ml/kg) preceded SP in all patients.

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Figure 1. Two-dimensional contrast echocardiography in patient with patent foramen ovale. (a) We noted the appearance of the contrast medium (in white) in the right atrium (RA). (b) The contrast medium has passed into the right ventricle (RV) but also into the left cardiac cavities (left atrium [LA]), left ventricle (LV) via a PFO.





Routine monitoring included electrocardiography (lead V5) and direct arterial blood pressure measurements through a radial artery catheter. Special monitoring for VAE included a Swan-Ganz 7F catheter and an infrared capnometer (Datex Normocap). The criteria confirming the diagnosis of VAE were both an increase in gradient between the capillary wedge pressure and the pulmonary artery pressure (PAP) sometimes associated with the aspiration of air microbubbles by the right atrial catheter and a fall in end–tidal Pco₂ (P_{et}Co₂). In each case of VAE a gentle, short duration bilateral jugular compression was applied to demonstrate the source of VAE, and N₂O was immediately discontinued until PAP and P_{et}Co₂ had returned to their initial values.

To detect PAE during the intraoperative course, visualization of air in the cerebral arteries and cardiac ischemia signs on ECG lead V5 were searched especially during episodes of VAE. In the immediate postoperative period a neurologic examination was performed to search for clinical deficits unrelated to the surgical procedure. In this last case the diagnosis of PAE could be confirmed by the presence of air with cerebral computed tomographic scan.

Results

Identification of a right-to-left shunting was observed in 22 patients (10%) on the preoperative 2D-CE. Because none of these patients had clinical evidence of true atrial septal defect, it can be assumed that the shunting of echogenic microbubbles occurred through a PFO. The shunting was noted in 15 patients during spontaneous ventilation, in 19 patients during coughing, and in all 22 patients after a Valsalva maneuver.

In seven patients the 2-D CE was of suboptimal technical quality and insufficient to rule out a PFO. No side effects were associated with the method.

Consequently, the SP was contraindicated in these 29 patients (13%). The procedure was conducted in the SP in the remaining 189 patients (126 posterior fossa interventions, 63 cervical laminectomies). Thirty-nine patients (20%) presented one or several episodes of VAE. The frequency of VAE was 13% in cervical laminectomies and 23% in posterior fossa interventions. During these episodes of VAE, no ECG changes were noted and no air bubble was visualized in the cerebral arteries.

During the postoperative period one patient without VAE episode presented a transient, slight quadraparesis related to a cervical cord ischemia attributed to intraoperative prolonged cervical flexion. All the other patients recovered uneventfully from anesthesia. No clinical neurologic deficit could possibly be attributed to a PAE especially in patients with episodes of VAE.

Discussion

The most likely cause of PAE is related to the passage of air bubbles through a PFO. The incidence of a PFO in the general population is reported to be 20–30% (4). Because VAE occurs in 30–40% of patients during seated neurosurgical procedure (2), the risk of PAE in the SP could be estimated close to 6–12% (1,2). However, the true incidence of PAE is unknown. The neurologic or cardiovascular sequelae due to PAE depend on the amount of air passing through the PFO and on the PAE route. All these considerations probably explain why PAE is not usually detected by clinical signs.

However, the PAE is a well known phenomenon that can be visualized using 2-D TEE during anesthesia in patients with a PFO during neurosurgical procedures in the SP (3). Disastrous outcomes from PAE have been reported in such patients (2). Therefore, the ability to identify preoperatively patients with a PFO, using 2-D CE, seems to be of the utmost importance (5).

In this study 22 patients with a PFO were detected, which represents a 10% incidence. Among these patients, 15 (6%) had a right-left shunting at rest during spontaneous ventilation. The sensitivity of the method can be improved by increasing the right-left shunting during coughing (6) (19 detected patients) and by the Valsalva maneuver (22 detected patients) (6). All patients with a detected PFO must be considered as having a "high risk" to develop PAE during VAE episodes. Avoidance of the SP in these patients should decrease the risk of VAE and consequently the risk of PAE with its complications.

The incidence of PFO detected in this study is comparable to that observed in healthy volunteers using the same method (7), but less than that reported in autopsy studies (4). In some cases of PFO, the passage of the contrast medium from right to left cavities is either impossible or insufficient to be detected by 2-D CE. This can be explained by variations in the size of PFO (1-19 mm diameter) (4) and by differences in the importance of the right-left shunting for each patient, either spontaneously or during coughing or the Valsalva maneuver. Consequently the occurrence of a PAE in a patient without a detectable PFO cannot be excluded, particularly during a spontaneous episode of massive VAE, in which both the volume of air embolized and the right-left shunting at the atrial level can be greater than during 2-D CE associated with coughing or the Valsalva maneuver. This phenomenon has already been observed by Cucchiara et al. (3) with 2-D TEE during surgery, who reported a patient in the SP who demonstrated a PAE intraoperatively during a spontaneous VAE, although no paradoxical contrast bubbles had been previously visualized. Therefore, in patients with no PFO detected by a preoperative 2-D CE, early detection of VAE must still be carefully monitored during neurosurgical procedures in the SP.

The incidence of clinical postoperative complications related to PAE is reported to be <1% in patients operated on in the sitting position (1). Therefore, it is not possible to conclude from this limited study that the absence of cardiac or neurologic complications is exclusively due to the preoperative detection of a PFO. However, because PAE occurs generally through a PFO, it seems likely that reducing the number of neurosurgical procedures in the SP in patients identified as having a PFO will decrease the incidence of PAE. Because PAE can be a lifethreatening complication, the cost of a preoperative 2-DCE appears justified. Two-dimensional contrast echocardiography is a safe, noninvasive method that can be helpful to identify the presence of atrial right-to-left shunting in all patients scheduled for neurosurgical procedures in the sitting position.

We thank Miss C. Bourassier for typing the manuscript.

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Letters to the Editor

Carbon Dioxide Detection and Esophageal Intubation

To the Editor:

Dr. Sum Ping's letter (Anesth Analg 1987;66:483) is extremely important in its implication, for in recent years the determination of end-tidal CO_2 has come to be widely accepted as the best method for determining proper endotracheal tube placement. The widespread use of infrared capnography and mass spectrometry in the operating room rests on the assumption that CO_2 , while abundant in alveolar gas, is virtually absent in stomach gas. We as anesthesiologists must respond to his concern, for if his interpretation is correct, we have placed far too much weight on this single measurement.

Dr. Sum Ping's conclusions raise two questions. First, how does the gas in the stomach accumulate so much carbon dioxide? Dr. Sum Ping postulates, "If enough alveolar gas is forced down the esophagus into the stomach during mask ventilation prior to intubation, the concentration of CO₂ in the latter may be similar to that in the alveoli." This suggestion appears simplistic, in that any alveolar gas forced into the stomach during mask ventilation will be diluted first with fresh anesthetic gases and subsequently with native stomach gas. Therefore, stomach gas, Pco₂ should not approach alveolar levels.

Second, we are puzzled by the waveforms submitted. As Dr. Sum Ping points out, the waveform of the first three breaths looks virtually normal before becoming flat very quickly. We agree, but assert that this graph simply does not represent a pattern of gas washout. In the first three breaths depicted in the waveforms, there was no change in end-tidal CO₂, followed by a precipitous drop to zero in breaths four to six. This pattern is not consistent with conventional washout curves and indicates that for the first three breaths no washout occurred! What happened between breaths three and four to account for this dramatic change?

Another explanation might be that the tube was initially properly placed in the trachea, but became dislodged between breaths three and four. Proper tube placement explains the measurement of consistent physiologic levels of CO₂ observed in the first three breaths. The rapid decrease in CO₂ in subsequent breaths followed displacement and resulted from dilution with gas from the mouth,

pharynx, and/or esophagus. As Murray and Modell have previously pointed out, inadvertent movement of the tube tip from the larynx to the pharynx produced distinctly different waveforms (1).

We suggest that our explanation provides a plausible interpretation of the facts as presented by Dr. Sum Ping and believe that the measurement of expired CO₂ remains the standard of reference in the determination of proper endotracheal tube placement.

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In Response:

Thank you for giving me the opportunity to reply to Dr. Salzarulo et al. In response to their first question, I do not believe that the alveolar gas forced into the stomach is diluted to any significant amount. After expiration, the pharynx, mouth, and area under the mask, up to the Y-connector in a circle system, contain expired alveolar gas. During this phase of ventilation, fresh gas does not cause any dilution in those areas because it normally goes to the part of the system with the least amount of resistance, i.e., to the reservoir bag. During the inspiratory phase of ventilation, the undiluted alveolar gas in the above areas will be the first to be forced, during positive pressure ventilation, down either the esophagus or the lung followed by fresh gas. As volume of gas in both the esophagus and lung builds up, the compliance of the esophagus decreases faster than that of the lung. This will lead to most of the fresh gas going to the lung, but some will leak out in a difficult mask case. Hence the gas going to the esophagus and stomach may consist mainly of alveolar gas. If alveolar ventilation is inadequate for any reason during a difficult situation, then Pco2 of alveolar gas may increase to 50 mm Hg or even higher. Also the Pco2 of stomach gas is never 0 mm Hg because of its good blood supply. For these

reasons, I believe that Pco₂ of esophageal and stomach gas may approach alveolar level.

To answer the second question, one would not expect a normal pattern of gas washout from the esophagus and stomach for the following reasons:

- There is a physiologic sphincter between the stomach and esophagus that makes movement of gas across it very unpredictable.
- 2. Because of the distensibility of the esophagus it is difficult to obtain a "good" seal with the cuff of a misplaced endotracheal tube. This will cause leakage of gas from the esophagus during and in between the inspiratory phase of ventilation. As a result, the volume of fresh gas entering the stomach is very variable.
- The 'end-tidal' Pco₂ with esophageal intubation does not reflect the Pco₂ of the stomach gas because the former will vary according to how much gas comes out of the stomach during the expiratory phase.

The letter also referred to the study by Murray and Modell, which concluded that no carbon dioxide could be measured if the endotracheal tube was placed in the esophagus. But that study was done on mongrel dogs, none of which required mask ventilation.

I maintain my original belief, but despite this limitation, which is pointed out so that anesthetists will observe the CO₂ pattern sufficiently, I still trust continuous end-tidal CO₂ measurement as a reliable way of determining proper tube position, provided one looks at the waveform again after several breaths.

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In Response:

I read with interest the case report written by Dr. Ping (Anesth Analg 1987;66:483) dealing with the problem of accidental esophageal intubation (1). Dr. Ping has noted that traces of carbon dioxide can be seen in a capnogram even if the intubation tube is placed into the esophagus. This finding was first published in 1983 in Acta Anaesthesiologica Scandinavica (2). The article includes a figure very similar to that published by Ping. The fact that carbon dioxide can be detected with esophageal intubation when expired CO2 has been forced into the stomach during prior mask ventilation was also mentioned in the review of Birmingham et al (3). However, end-tidal CO2 measurement remains the most reliable method for detection of accidental esophageal intubation. This is because after a few breaths, the CO2 in the stomach is diluted and the waveform will very quickly become flat (1)

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Stressed Children?

To the Editor:

Davis et al. (1) provided useful information on the pharmacokinetics of sufentanil in infants and young children (ASA II and III) undergoing cardiac surgery. However, the sufentanil was given *after* insertion of the intravenous catheter, endotracheal tube, and arterial catheter. The children were intubated after being given nitrous oxide (percentage not specified) and metocurine. Halothane was added only if there was difficulty with venous or arterial cannulation. The children received a preoperative medication of morphine, secobarbital, and atropine. Infants younger than 1 year were given only atropine.

Perhaps the children were adequately anesthetized during intubation. The data to assess this was not given. The hemodynamic baseline data presented were obtained the day before surgery. The initial intraoperative hemodynamic data shown were obtained 1 min after sufentanil anesthesia. The catecholamine levels were much higher than those seen in adults undergoing cardiopulmonary bypass (2,3). Without knowledge of the catecholamine levels before induction, it cannot be determined if the elevated levels reflected the basal state of children with congenital heart disease or a stress response. The first samples were attained before sufentanil was administered, but this information was not presented.

I find it ironic that the stress response to cardiovascular procedures was studied after intubation on minimal anesthesia. As a mother, I would not consent for my child to participate in this study. I wonder if the desire to perform a "pure" drug study interfered with the optimal patient care?

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In Response:

Although many sedative-hypnotic agents, narcotics, and muscle relaxants have been extensively studied in adult

surgical patients, it is equally important to document the safety, efficacy, pharmacokinetics and pharmacodynamics of these agents in infants and small children. We are quite sensitive to the issue of balancing good pharmacologic experimental design with the practicalities of optimal anesthetic care for studies in infants. Because it is difficult to place intravenous and arterial catheters in awake, struggling infants, "pure" pharmacologic studies of intravenous drugs are rare. We and others have preferred to sedate or anesthetize infants before inserting vascular catheters or before tracheal intubation. Indeed such was the case in our sufentanil study although the manuscript is in error in this regard. In the infants in whom anesthesia was induced with nitrous oxide and oxygen (5 of 20), sufentanil was given before, not after the trachea was intubated (1). In the remaining infants (15 of 20) in whom arterial or venous access was difficult, the trachea was intubated during nitrous oxide-oxygen and halothane anesthesia. Review of our anesthetic records indicates that no infant was stressed as evidenced by unacceptable changes in heart rate and blood pressure during the intubation.

The main purpose of the catecholamine determinations were to show relative changes in cathecholamine concentrations during different periods of surgery. The issue of what constitutes a baseline value is very difficult in pediatric anesthesia. Hickey and Hanson (2), in their comparative study of sufentanil and fentanyl in children undergoing corrective heart surgery, commented that their preinduction baseline values for heart rate and blood pressure were somewhat higher than expected because of patients' underlying congestive heart failure, light premedication, and agitation. We are not convinced that obtaining blood samples from an agitated and/or frightened child before the induction of anesthesia (whether this is done in the operating room or in the patient's ward) represents a baseline level. Because of the differences in techniques used for induction, N2O/O2 sufentanil and N2O/O2 halothane, we elected to use as a basis for reference catecholamine levels 1 min after sufentanil infusion. We had a great deal of difficulty with hemolysis in the first 10 patients. Unfortunately, the five patients in whom anesthesia was induced with nitrous oxide-oxygen and sufentanil were in this group and, therefore, the change in catecholamine levels with intubation could not be adequately assessed.

Dr. Dehring correctly notes that the catecholamine levels observed in our series are higher than those reported in adult patients undergoing cardiopulmonary bypass (3,4). Presently, little data are available on the anesthetic effects of catecholamines in children undergoing open heart procedures. However, Moore et al. (5), in a similar study on the hemodynamic and anesthetic effects of sufentanil in older pediatric patients undergoing cardiac surgery, reported catecholamine concentrations in the range similar to the levels reported in our study. In addition, in infants receiving high dose fentanyl (after a nitrous oxide-oxygenhalothane induction) for cardiac surgery, we noted catecholamine levels comparable to those reported with sufentanil (personal observation). Whether the elevated

catecholamine levels observed in infants and children are a result of the underlying pathophysiology of congenital heart disease or whether these differences in catecholamine levels represent differences in premedication, adjunct anesthetic agents, and anesthetic techniques, or represent differences in assay techniques, remains to be determined.

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Megaloblastic Anemia and Brief Exposure to Nitrous Oxide—A Causal Relationship?

To the Editor:

Neurologic dysfunction secondary to exposure to nitrous oxide, which unmasked previous vitamin B12 deficiency, has been reported in two patients (1). Recently, we encountered at our institution a patient with a history of a resolved vitamin B12 deficiency, in whom megaloblastic anemia reccurred after a brief anesthetic exposure to nitrous oxide. The patient was a 76-yr-old woman with a history in the mid-1960s of a short-bowel syndrome secondary to the removal of an 85-cm segment of small bowel, including part of the terminal ileum. After this operation, vitamin B12 deficiency developed and required treatment, but the anemia had resolved and the patient had not been taking supplements at the time of her present admission.

The patient was admitted for an anterior cervical fusion. Preoperative hematocrit was 43.9%, RBC 10 \times 5 cmm = 3.84, MCV 114 μ^3 (normal 79–99), MCH 38.3 $\mu\mu g$ (normal 27–31), and MCHC 33.5 vol % (normal 32–36). Anesthesia was induced with thiopental 400 mg and fentanyl 3 $\mu g/kg$, followed by atracurium 30 mg IV, and was maintained with nitrous oxide 60% in oxygen, isoflurane, and fentanyl. The operation lasted 2 hr and 15 min. With a hematocrit of 41.3% and no postoperative complications, the patient was discharged from the hospital.

Subsequently the patient complained of increasing fatigue, pain, numbness, and weakness in both arms. Five months after operation, she was seen by her medical internist, who found her hematocrit was 30.3%, MCV 111 μ^3 , MCH 41.4 $\mu\mu$ g, MCHC 37.3 vol %, and vitamin B12 level <100 pg/m. She was treated with vitamin B12, 1 mg IM four times a month, and 1 month later her hematocrit was 40.2 vol %, MCV 96 μ^3 , MCH 32.8 $\mu\mu$ g, and MCHC 34.1 vol %

Nitrous oxide can inactivate the vitamin B12 group of methionine synthetase. Although our patient was not anemic preoperatively, her indexes showed macrocytosis and probable marginal absorption of vitamin B12 from her short bowel. Though exposure to nitrous oxide for our patient's anesthesia was brief, her probable low levels of vitamin B12 might have been oxidized enough to depress methionine synthetase activity. Because her ability to absorb vitamin B12 would have been poor, the amount needed to replenish the stores might not have been sufficient; thus, megaloblastic anemia could have developed.

Though we cannot be certain this episode resulted from exposure to nitrous oxide, it may be wise not to expose patients with a history of pernicious anemia or certain malabsorption problems to nitrous oxide, even briefly. This type of effect may be more common than originally suspected (1).

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Book Reviews

Physiology of Oxygen Radicals

Aubrey E. Taylor, Sadis Matalon, and Peter A. Ward, eds. Bethesda: American Physiological Society, 1986, 301 pp, \$49.50.

The rapid transition of the biology of free radicals from an esoteric topic of interest to a subject of major importance to a wide variety of biomedical workers is well exemplified by this book. Phenomena as diverse as biologic aging, normal defense mechanisms against pathogenic bacteria, hepatic toxicity of chloroform, pulmonary oxygen toxicity, myocardial damage following reperfusion after infarction, and posthypoxic encephalopathy are only a few of the occurrences that have a common etiology in the production and action of oxygen-derived free radicals.

The first chapter presents the basic biochemistry of oxygen free radicals and discusses the means by which the living organism blocks their toxic actions, whereas the second chapter deals with currently available means of assessing free radical-induced tissue damage.

That a considerable portion of the subsequent chapters are devoted to pulmonary oxygen toxicity is not unreasonable because the lung is a target organ exposed to the highest partial pressure of oxygen. The text details information dealing not only with numerous ways in which pulmonary oxygen toxicity may be produced, but also gives information dealing with potential means of facilitating repair of pulmonary tissue after toxic exposure has occurred. The last few chapters deal with other phenomena in which free radical physiology plays a significant role. Among these are pathologic responses of the cerebral circulation such as those that occur with acute severe hypertension and experimental brain injury, the role of oxygen-derived free radicals in ischemia-reperfusion injury in a wide variety of organs including the central nervous system, gut, heart, liver and skeletal muscle, and the effect of oxygen radicals on the aging process.

The manuscript is well organized with a clear summary at the beginning of each chapter. The illustrations are well done and facilitate understanding of the material presented in the text. This book can be read at many levels ranging from that of the interested practitioner who by selecting a few specific chapters will gain basic knowledge of a burgeoning topic of investigation, to the scientist wishing to obtain up-to-date information on the technology and many exciting topics of research dealing with oxygen free radi-

cals. Although not always easy reading (because the topic is complex and requires background knowledge), the book will reward those who are willing to take the time to peruse it.

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Anesthesiology and the Law

J. Douglas Peters, Keith S. Fineberg, Donald A. Kroll, and Vincent Collins. Washington, D.C.: Health Administration Press, 1983, 397 pp.

Given the increased attention to malpractice issues in both the lay and the medical press, this book will be of interest to all who interact in one way or another with patients, physicians, or hospitals. Although both medicine and the law have undergone changes in the 4 years since publication, the book remains an excellent reference source for all those with an interest in the subject. Two of the authors are attorneys with diverse experience in the medicolegal world and the other two are physicians who have between them wide experience in both health care administration and anesthesiology.

The book is divided into three parts. Part I deals with the general issue of liability. After outlining the dimensions of the malpractice problem generally and specifically in terms of anesthesiology and presenting a summary of the history of the legal theories involved, current concepts of liability, their relevance in the medical setting, and the elements of the standard medical malpractice case are discussed. The authors have succeeded in conveying the concepts very clearly, in point form, with ample discussion liberally interspersed with case illustrations. The remainder of part I is dedicated to a discussion of concepts such as vicarious liability, the question of nurse anesthetists, the liability of hospitals, and the various defenses that may be brought to bear in the face of a malpractice suit such as contributory negligence, assumption of risk, release from liability forms, and the statute of limitations. The final chapter in part I deals with the more practical aspects of malpractice litigation. Terms such as interrogatories, complaints, depositions, and others are explained and illustrated.

Part II deals with the regulation of the medical industry. This is an extremely complex area of the law, given the multitude of jurisdictions extant in the country. The authors deal with individual physician licensure, PSROs, specialty certification, regulation of nurse anesthetists, and the regulation of competing professions. The chapter on hospital regulation is extremely well written and should be of interest to all who wonder how hospitals govern themselves, the nature of their corporate status and the "chain of command" in the hospital. JCAH standards for both hospitals in general and anesthesia services in particular are discussed.

Part III deals with anesthesia practices and applies the principles discussed in parts I and II to anesthesiology. The concept of standard of care, so central to the determination of liability in negligence actions in general, is applied here to our speciality. The sources of anesthesia standards of care used in the text include published guidelines of the American Society of Anesthesiologists (ASA) interpretations and customary practice, as written by medical authors, and appellate court reports of jury-trial decisions. The authors acknowledge that this section in particular will be controversial and that there will be those who believe that articulating standards of care are antithetical to the art of practicing medicine. However, given the fact that malpractice does occur and that the courts and arbitration boards need guidance in coming to their decisions, some standards have to exist, if only for the guidance for those of us who want to avoid pitfalls in our practice. The creation of an Ad Hoc Committee on Standards by the ASA in 1985 in part reflects this need.

This multiauthored text is extremely well written, easily comprehensible, and free of overdramatization so commonly seen in the legal-medicine literature. In a field in which law, medicine, and society often interact in an adversarial atmosphere, I found the lack of carping a refreshing departure from the all too frequent finger pointing that develops when the subject of medical malpractice arises.

The consistent writing style, liberal use of case illustrations, and extensive bibliography are particularly useful. Although the authors warn against using this text as a substitute for competent legal counsel, the text will be of inestimable value as a referral and resource book for those involved in the practice of medicine, law, or hospital administration.

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Anesthesiology Clinics of North America Volume 5, Number 1. March 1987: Outpatient Anesthesiology. Herbert D. Weintraub, and Marie-Louise Levy, eds. Philadelphia: WB Saunders, 1987, 274 pp, \$25.95, single issue; \$60.00, four issues. This issue of Saunders' quarterly hardbound publication is edited by two members of the faculty of George Washington University's Department of Anesthesia, which has a long experience in outpatient anesthesia for both adults and children and many of the chapter authors are George Washington faculty members. Other acknowledged experts have also contributed to this volume, including Leroy D. Vandam, MD, on the history of ambulatory anesthesia.

This book demands careful reading. It contains a great deal of useful information, much of it learned by the authors during many years of caring for outpatients, and some of it not available anywhere else. Unfortunately, it also demands *critical* reading and evaluation of some of the recommendations in the light of one's own practice and common sense. It is a volume which should be accessible in departmental or institutional libraries but will not become *the* textbook of outpatient anesthesia, a hope I held when I first saw the title.

The 13 chapters are of remarkably uneven quality. Two are acknowledged rewrites of material that appeared elsewhere. Several others are little more than catalogs or lists of drugs, problems, or other "things to think about," with neither interpretation nor sufficient information to be of use to the practitioner. References to the impending release of midazolam in the United States and the absence of pulse oximetry and end-tidal carbon dioxide monitoring in the list of recommended parameters raise questions about publication delays for a volume dated March 1987. Internal inconsistencies such as conflicting recommendations about the need for an assistant in performing a caudal block on an anesthetized child (pp 53, 55) and misidentified abbreviations (e.g., MAC, maximal acceptable concentration) trigger a sense of discomfort in the reader seeking authoritative guidance and a better way. The reader of a specialty publication like Anesthesiology Clinics of North America is entitled to a certain amount of analysis and integration. Unfortunately, these are unevenly distributed throughout

Several chapters discuss "how we do it," a definite attraction in a book of this type. Those chapters that review the arguments pro and con, the information necessary to make an intelligent choice of anesthetic technique and *then* go on to describe a particular method are quite valuable. They share much more of the experts' knowledge with the reader than does the straight cookbook approach. The chapters on pediatric anesthesia (both general and regional) and the chapter on regional anesthesia for adult outpatients are good examples of this writing (and teaching) style.

The discussion of the outpatient management of pain is necessarily superficial, but it addresses one of the fastest growing segments of the mushrooming practice of outpatient anesthesia. Again, the information is presented in a clinically useful way. Other chapters include presentations of postoperative course and follow-up, complications, quality assurance activities, nursing considerations, and legal considerations. The inclusion of sample documents from different institutions is valuable.

The approach to the airway under general anesthesia

that is described in the chapter "Dental Outpatient Anesthesia" differs from traditional practices. Many anesthesiologists would take issue with the techniques espoused. The authors place great stock in judgement and experience, but do not lead the reader through the thought processes necessary to acquire that judgement.

All in all, this is a useful volume. It does not answer all of the questions about outpatient anesthesia, nor is the right answer provided for all the questions answered. However, this volume does bring together the acquired wisdom of some excellent, experienced clinicians, and provides those of us facing clinical problems every day with more information to apply to answer our own questions.

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Recovery Room Care, 2nd Edition.

Jacob S. Israel and Thomas J. De Kornfeld, eds. Chicago: Year book Medical Publishers, 355 pp, \$44.00.

This is the second edition of a multiauthored book originally published in 1979. New chapters include one on financial problems in the recovery room and another on the psychiatric implications of recovery room care. Nearly 50% of the book is devoted to the logistic and administrative aspects of recovery room care. Because of that, the book is heavily oriented toward administration. Nevertheless, the patient care aspects covered in the book are well done and represent typical problems in recovery room care.

The first two chapters are a good review of the overall status of the recovery room and a very insightful review of the design characteristics of recovery rooms. The design chapter is particularly well written with a large amount of practical information regarding architectural issues. Although the section on monitoring and other equipment is a good review, there are two areas that should have received more attention. Pulse oximetry is not covered at all and the description of ventilating devices certainly could have been more thorough.

The chapter that deals with economic issues in recovery room care is extremely well written and very timely. The chapter that discusses criteria for patient care, including nursing procedures and policies, contains no review of the factors that affect recovery from the various anesthetic drugs and techniques used today. The first chapter, which actually deals with medical aspects of patient care, is titled, "Emergency Diagnosis and Treatment," and deals predominantly with acute cardiovascular problems in the recovery room. The next chapter is an excellent review of respiratory disorders except for the omission of any description of the use of oximetry in the detection of arterial hypoxemia.

Thorough reviews of fluid and electrolyte balance in the postoperative patient's surgical care are presented. How-

ever, the postcardiac surgery patient is not always managed in recovery rooms.

Psychiatric implications of recovery from surgery and the management of pain and delirium is the only discussion about pain management in the book. However, this discussion is not entirely thorough in that it fails to present all of the available options. For example, there is no mention of the use of epidural and intrathecal narcotics, which have received increasing use in patients recovering from anesthesia. The chapters on pediatrics and neurosurgical considerations are excellent reviews. The final chapter on legal considerations in the recovery room is timely and relevant.

In summary, this is a very good book whose strengths lie in the areas of administration and management of recovery rooms. Its major weakness lies in several significant omissions. It is an excellent addition to an anesthesia library and is especially useful for individuals interested in the design and management of a modern recovery room.

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Common Problems in Cardiac Anesthesia J. G. Reves and K. D. Hall, eds. Chicago: Year Book Medical Publishers, 1987, 551 pp, \$46.95.

The editors have undertaken an ambitious and demanding project and have succeeded admirably. They have not only produced a textbook style new to the field of anesthesiology, but one that is very readable and informative. The ambitious scope of the project is indicated by the fact that the list of 62 authors reads like a Who's Who of cardiac anesthesia.

Each individual chapter is structured beginning with a concisely stated clinical problem followed by an author's analysis of the clinical situation presented by that scenario and (most of the time at least) a clearly described clinical approach to the resolution of that problem. The final section of each chapter is a discussion of the pathophysiology of the clinical problem and the theoretical basis for the therapeutic approach as it was outlined. Although the vast majority of the chapters succeed nicely in the first three areas, the variation in quality of the individual contributions is most obvious in the discussion sections. As the editors point out in the preface, it was difficult for some of the authors to commit to a single approach to the clinical problem. The result is that some of the authors treated their topics in a rather superficial fashion, almost as if saying, "this is how you should approach this problem because this is the approach that I use." Fortunately, this appeared in a small minority of chapters. Much more commonly the authors supported their positions with appropriate reference to experimental and clinical literature. In particular, I would cite the chapters by Govier, Hickey, Torpey, Buffington, and Lowenstein as exemplifying the latter approach, although numerous others could equally be cited.

As might be expected in a book with as many contributions as this, there is some overlap in the discussions. For example, in the section on congenital heart disease, two chapters have deep hypothermia as a primary focus and two chapters focus on problems associated with arterial air embolism as a consequence of cardiopulmonary bypass. This difficulty is, however, rather trivial because it may actually confer the advantage of two expert opinions relating to the same topic.

While this book may not be encyclopedic in its coverage, that was not its intent. The stated intent was to expose the audience "to a number of common clinical problems . . . not so common as to occur every day in every patient, but rather . . . perhaps once a week in a busy clinical practice." In this goal the book is a definite success and should at least be available in a library that is readily accessible to any one who deals with cardiac surgical patients on a less than continuous basis. Perhaps more importantly, the book should definitely become part of the required reading list for anesthesiology trainees, particularly in the subspecialty area of cardiac anesthesia. The book sets a good example for subsequent efforts in other areas.

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Cardiac Anesthesia, 2nd Edition

. A. Kaplan, ed. Orlando: Grune & Stratton, 1987, 1122 pp, \$125.00.

The first edition of *Cardiac Anesthesia* was written by an enthusiastic, motivated cardiac anesthesia group from Emory. In the second edition, Dr. Kaplan has coordinated the work of many other writers. The product is a well ntegrated compendium of knowledge, perhaps less enthusiastic than the first edition, but complete nevertheless.

Some chapters present a well referenced body of knowledge but lack personal conclusions on what the facts mean for the clinician, a responsibility that I think is mandatory for an expert in any field. For example, in the chapter on coronary circulation, the reader is left searching for guidance as to whether certain drugs should or should not be used.

Basic pharmacology and its application to the cardiac patient are well covered. It is expanded in subsequent chapters beginning with an informative and up-to-date chapter on opioids. Important details have emerged in the past several years and the contrast with the usual properies of opioids is comprehensively presented. Precise and informative selection of the nonopioid intravenous aneshetics that are often used is easy to read, the authors' enthusiastic opinion of the benzodiazepines is refreshing if only to disagree with. There is little bias that is not presented without the opposite argument and the reader eaves the chapter well informed.

Monitoring is very well covered in specific chapters but

also throughout the books, with many future options offered that may become standards. There is an excellent review of echocardiography. This chapter begins at the simplest level and with easy informational steps allows the uninitiated to familiarize himself with concepts that allow him to enter the technological advances of the past 3 years.

A detailed chapter on preoperative considerations expands into techniques used in definitive cardiologic evaluation. There are sets of rules to follow with check-off lists for completeness. This chapter is a must for policy and procedure committees.

Perioperative arrythmias is one of the most comprehensive chapters, written with uncomplicated and clear description. Time is spent on each drug in proportion to its clinical importance.

One of the mainstays of retaining a reader's attention to a textbook is to give him or her the feeling of progressing. Good editorial selection and planning keep this book interesting. There is inevitably some overlap of topics but where this occurs it comes over as a reemphasis of the importance of that topic, assuring the reader that the repetition is for his or her benefit. Editorial discipline was not fully maintained in the illustrations. Some are excellent and original. Many are, however, faint copies and are often too small to focus the reader's attention, especially in the complicated clinical figures of Volume 2.

From a thoughtful, broader look at CABG surgery we next visit the world of valvular disease. This chapter is delightful. The English is excellent and the information so complete there is hardly any need to read around the subject. The theme of the second volume is distilled into this chapter: practical cardiology and its relation to anesthesia. A tremendous effort went into writing the congenital disease section. There is a substantial introduction to the specific differences and knowledge required to understand pediatric cardiac patients. Aortic surgery is concisely treated and there is special emphasis on the preservation of spinal cord integrity. Here, as in chapters on reoperation and electrophysiologic procedures, the authors' vast experience add reality to the subject.

Pacemakers are made understandable and, again, the reader is assured of a meaningful working knowledge to ensure his credibility in discussions about pacemakers. Discussion of cardiac transplantation needed to be more detailed.

Experience allows the author of the cardiopulmonary bypass section to include useful opinions and still maintain objectivity with the information currently available. The same can be said about cardiac preservation, which complements the above chapter, with an emphasis on cardioplegia. An important chapter underscoring the strategic position of the often ignored right ventricle shows the dilemma of diagnosis and treatment. Serious questions are explored if not answered. Circulatory assist devices are becoming more prominent in many cardiac anesthesiologists' days and nights. The various modalities are well described though the management implications are scantily addressed.

BOOK REVIEWS ANESTH ANALG 203

These two volumes should be read by all anesthesiologists, at least in part. The implications of taking care of so many older patients with ever decreasing cardiac status should not be lost to anyone in anesthesiology. The volumes are a must for cardiac anesthesiologists, but bring your reading glasses because the print has approached microfilm dimensions.

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Oxygen Transport in the Critically Ill James V. Snyder and Michael R. Pinsky, eds. Chicago: Year Book Medical Publishers, 1987, 554 pp, \$74.95.

The authors state that "our goal throughout this text is to present the physiologic and therapeutic complexities of critical care in paradigms that incorporate recent insights and prepare the reader for the anticipated increasing focus on regional pathophysiology and treatment." With this in mind, they have organized the book so that "the structure of the book is designed to encourage analysis of overall oxygen transport before assessment of individual components or focal compromise."

The text is divided into six parts, starting with three sections that review the basic physiologic concepts of "oxygen supply and demand," "regulation of oxygen transport" by autonomic, pharmacologic and neurohumoral mechanisms, and "cellular oxygenation." The concepts are generally well explained in the text, and equations, diagrams, illustrations, and radiographs are used effectively for clarification and emphasis. An index has been included that facilitates location of specific topics of interest, and references are present at the close of each chapter. Case reports are interspersed throughout in order to relate physiology to patient care and to demonstrate the clinical application for the concepts discussed, e.g., the importance of hemoglobin in oxygen transport and clinical conditions associated with altered oxygen consumption. An effort has been made to tie the chapters together and to avoid redundancy by cross-referencing to other chapters. There is occasional uneveness in writing style which does not, however, diminish the overall readability of the vol-

The next three parts are more clinically oriented and, as the authors state, "throughout the volume we have tried to present a clinical perspective informed by basic physiologic concepts." These sections discuss "clinical evaluation of oxygen transport" by a variety of monitoring and imaging techniques, "ventilatory support: physiology and technique," and "circulatory support." Controversies in the existing literature are presented for several topics, such as the clinical correlations for hemodynamic monitoring and the interaction of ventilatory support and changing intrathoracic pressure with the failing circulation; these are reviewed and discussed with balanced perspective and reasoning followed occasionally by recommendations and opinions. Pulse oximetry, now routinely employed by anesthesiologists, is perhaps a sufficiently recent development to explain its absence from this text.

This book has effectively collected information in such a way as to present the multifaceted interrelations between the concepts of oxygen transport and the care of the critically ill patient. Although these concepts may be applied to patients being cared for by an anesthesiologist, there is very little direct or specific consideration of anesthetic management itself of the critically ill patient. Although the emphasis is on medical inpatient rather than on postsurgical care, any clinician or physician-in-training with responsibilities for critically ill patients, whether it be in the operating room or in the intensive care unit, would find portions of the book useful for its themes and insights as well as worthwhile and enlightening reading.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Benumof JL. <u>Anesthesia for Thoracic Surgery</u>. Philadelphia: WB Saunders, 1987, 521 pp, \$75.00.

Corssen G, Reves JG, Stanley TH. <u>Intravenous Anesthesia and Analgesia</u>. Philadelphia: Lea & Febiger, 1987, 334 pp, \$48.50.

Frost EAM, ed. <u>Practical Neuroanesthesia</u>, Anesthesiology Clinics of North America, Vol. 5, No. 3. Philadelphia: WB Saunders, 1987, 230 pp, \$25.95 single issue or \$60.00 for four issues/annual subscription.

Gravenstein JS, Paulus DA. <u>Clinical Monitoring Practice</u>, 2nd Ed. Philadelphia: Lippincott, 1987, 446 pp, \$49.50.

Graybar GB, Bready LL, eds. <u>Anesthesia for Renal Transplantation</u>. Boston: Martinus Nijhoff, 1987, 272 pp, 553.50.

Kaufman L, ed. <u>Anaesthesia Review 4</u>. New York: Churchill Livingstone, 1987, 234 pp. 527.75.

Paull JD, Robinson GD, eds. Third Report of the Victorial Consultative Council on Anaesthetic Mortality and Morbidity 1985. Melbourne, Australia: Health Department Victoria, 1986, 34 pages.

Roizen MF, ed. <u>Anesthesia for Patients with Endocrine Disease</u>. Anesthesiology Clinics of North America, Vol. 5, No. 2. Philadelphia: WB Saunders, 1987, 462 pp, \$25.95 single issue or \$60.00 for four issues/annual subscription.

Thys DM, Kaplan JA. The ECG in Anesthesia and Critical Care. New York: Churchill Livingstone, 1987, 267 pp, 524.00.

Errata

- Finucane BT, Hammonds WD, Welch MB. Influence of Age on Vascular Absorption of Lidocaine from the Epidural Space. Volume 66, Number 9, September 1987, pp. 843–6.
- The authors wish to inform readers of the following: In Table 2, C_s max was expressed as milligrams (mg/ml), which should have been micograms (μ g/ml).
- Snyder AR, Ilko R. Topical Nitroglycerin for Intraoperative Penile Turgescence. Volume 66, Number 10, October 1987, pp. 1022–3.
- The authors wish to inform readers that in reference to the dosage of nitroglycerin administered IV, the units should be micrograms (μg), not milligrams (mg).
- Watanabe S, Sakai K, Ono Y, Seino H, Naito H. Alternating Periodic Leg Movement Induced by Spinal Anesthesia in an Elderly Male. Volume 66, Number 10, October 1987, pp. 1031–2.
- In this article, "plantar flexion" should read "dorsiflexion"; "dorsiflexion" should read "plantar flexion."
- Shulman MS, Wakerlin G, Yamagichi L, Brodsky JB. Experience with Epidural Hydromorphone for Post-Thoracotomy Pain Relief. Volume 66, Number 12, December 1987, pp. 1331–3.
- The authors wish to inform readers that on page 1333, the dose of hydromorphone should read, "1.25–1.5 mg," not "12.5–1.5 mg."



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The safety of Tracrium has not been established in patients with bronchial asthma

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended: initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of > 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure with 4.8% and an increase in heart rate. At doses < 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported. General: allergic reactions (anaphylactic or anaphylactic) which, in rare instances, were severe (e.g., cardiac arrest); Musculoskeletal inadequate, prolonged block; Cardiovascular hypotension, vasodilatation (flushing), tachycardia, bradycardia; Respiratory: dyspnea, bronchospasm, laryngospasm; Integumentary: rash, urticaria, injection site reaction.

¹Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*, Orlando, Grune & Stratton, 1984, p. 98.

²d'Hollander A, Luyckx C. Bravis L: Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery. Lack of age-related effects. *Anesthesia* 1983;59:237—240

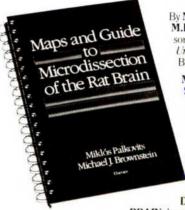
³Duvaldestin P, Saada J, Berger JL, et al: Pharmacoxinetics, pharmacodynamics and dose response relationships of pancuronium in control and elderly subjects. *Anesthesia* 1982;56:36—40.

⁴d'Hollander A, Massaux F, Nevelsteen M: Age-dependent dose-response relationship of Org NC45 in anesthetized patients. *Br J Anaesth* 1982;54:653—657.

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Maps and Guide to Microdissection of the Rat Brain



By MIKLÓS PALKOVITS. M.D., PH.D., D.SCI., Professor of Anatomy, Semmelweis University Medical School, Budapest, Hungary

MICHAEL J. BROWN-STEIN, M.D., PH.D.,

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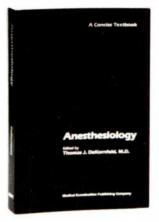
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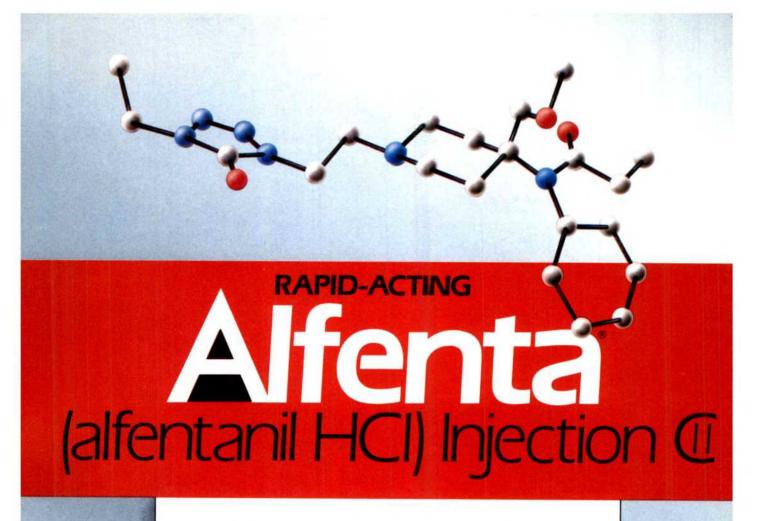
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'As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

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AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

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DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing altentanil hydrochloride equivalent to 500 µg per ml of altentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL AMESTHETIC AGENTS AND IN THE MANAGEMENT OF PRESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPICID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY

MOST CONTINUE WELL AT LEX SURGERY
ALFENTA (altentani hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal
muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually doserelated. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce
muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opinids.
ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing doswof a neuro-muscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simulta-neous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovancular status.

Adequate facilities should be available for postoperative monitoring and ventilation of patients—administered

ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiralory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNII MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (altentanii hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined

on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in gariatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative receivery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may pro-

duce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation.

required should be considered in the salaction of a neuromuscular blocking agent.
Following an enesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end

Respiratory depression caused by opigid analogsics can be reversed by opigid antagonists such as Respiratory depression cause by opioid analystics can be reversed by opioid analystics such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the dura-tion of the opioid analgesia is accompanied by respiratory depression and diminished sensitivity to CD₂ stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further after postoperative response to CD₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and

maintained in the absence of stimulation prior to discharging the patient from the recovery alea.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease. decreased respiratory reserve or potentially compromised respiration. In such patients, opicids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be inistered with caution due to the importance of these organs in the metabolism and exception of ALFENTA. Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular

ortig interactions: both the magnitude and obration to cellara hervice system and control sections are detects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhallation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma

clearance and prolong recovery Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutakinos or induction of the produced in the produced dominant lethal mutations. The Ames Salmonella typhimurium metabolic activating testialso revealed no

Prepnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when gives in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased montality) following

prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENIA in rats or rabbits.

There are no adequate and well controlled studies in pregnant women. ALFENIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery

Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant is of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is a administered to a

Pediatric Use: Adequate data to support the use of ALEFNTA in children under 12 years of age are not

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are excensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUT. ONS on the management of respiratory depression and skeletal muscle rigidity Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arthythmias and hypotension

have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and The reported incidences of adverse reactions issted in the following table are derived from controlled and open clinical virals involving IRIS patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enfurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in Clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients: undergoing gynecologic surgery

	ALFENTA (N — 785)	Fentanyl (N — 243)	Thiopental Sodium (N — 66) %	Enflurane (N — 55)	Halothane (N — 18)	Saline Placebo* (N — 18)
Gastrointestinal Nausea Vomiting	28 18	44 31	14 11	5 9	0	22 17
Cardiovascular Bradycardia Tachycardia Hypotension Hypertension Arrhythmia	14 12 10 18 2	7 12 8 13 2	8 39 7 30 5	36 7 20 4	0 31 0 6	0 11 0 0
Musculoskeletal Chest Wall Rigidity Skeletal Muscle Movements	17 6	12	0 6	0 2	0	0
Apnea Postoperative Respiratory Depression	7 2	0 2	0	0	0	0
CNS Dizziness Sleepiness/ Postoperative Sedation	3 2	5 8	0 2	0	0	0 6
Blurred Vision	2	2	0	0	0	0

From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryrgospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug sub-stance that can produce drug dependence of the morphine type and therefore has the potential for being abused

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{bo} of ALFENTA is 43.0-50.9 mg/kg in rats. 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intrarenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

ite to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanii hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely

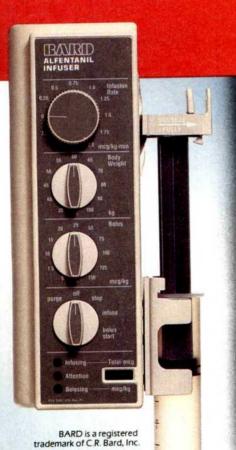
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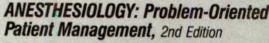
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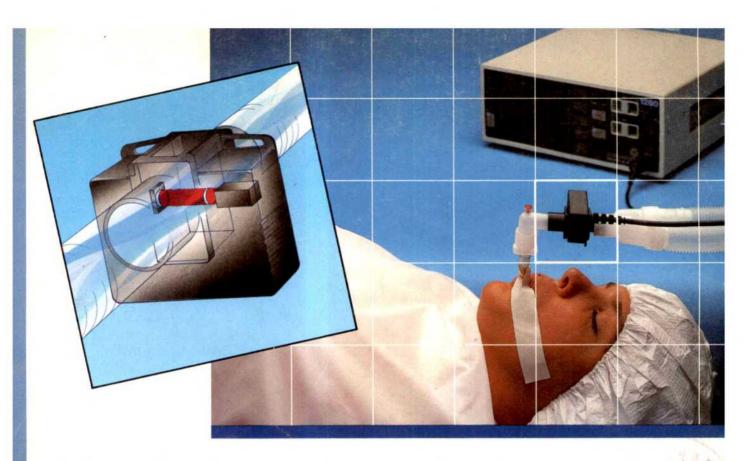
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Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infu-sion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

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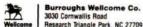
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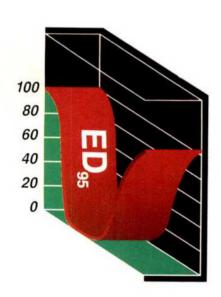
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Brief Summary

ald be used only by adequately trained individuals familiar with its actions, characteristics, and hazards

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infu-sion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

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¹ Hughes R: Atracurium: An Overview. *Br J Anaesth* 1986 58:2s-4s.

² Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*, Orlando, Grune & Stratton, 1984, p 98.

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Journal of the International Anesthesia Research Society

INTRAOPERATIVE PROCESSED EEG AND OUTCOME RESPONSES DURING CARDIOVASCULAR BYPASS PROCEDURES

Authors:

D Adcock, M.D., MS Albin, M.D., M.Sc. (Anes.), J Monts, M.D., R.R. Ritter, M.D.

Affiliation: Department of Anesthesiology, University of Texas Health Science Center at San Antonio. 7703 Floyd Curl Drive, San Antonio, Texas 78284-7838

Introduction: Neurological and behavioral dysfunction following extraocrporeal circulation for cardiovascular procedures has been described after surgery for valvular and congenital defects and coronary artery bypass grafts (CABG). The neurological complications have involved encephalopathy, stroke, altered mental states, and peripheral neuropathy, with incidence rates ranging from 3.85-165. The electroencephalogram (EEG) has been a useful tool in helping to detect the time of onset of intraoperative, intracranial ischemic changes, but has been limited in its use as a routine monitoring tool because of cost and the need for technical help and a proficient electroencephalographer. Recent advances in the development of the processed EEG have given us the opportunity to simplify the monitoring procedure with relatively inexpensive equipment that generates hard copy and does not necessitate an adjunct of technical and professional personnel. The aim of this retrospective study is to evaluate the intraoperative EEG in a series of patients with open heart procedures for valvular and coronary artery disease and to determine the effects of these responses on immediate outcome.

| Materials: Informed consent was obtained for all patients in this retrospective study. During the past two years, 103 patients having open heart surgery were monitored using the processed EEG for valvular, CABC and combined CABG-Carotid endarterec tomy (CEA) and they are the subjects of this study. We used a commercially available EEG monitor (Neurotrac with compressed spectral array capability (CSA). This unit presents two channels of EEG-CSA data (left and right cerebral hemispheres) recorded from the placement of five electrodes. The reference electrode is placed in the middle of the forehead along the placement of five electrodes. The reference electrode (-) of each channel attached immediately above the ear or behind the ear on the mastoid bone. Anesthesia consisted of high dose fentanyl diazagam, pancuronium, isoflurane, enflurane, or ha

left hemisphere. After bypass, the EEG- CSA activity again decreased to the preoperative and rost-CEA level. The patient in Case 5 suffered a rapid loss of left hemispheric EEG-CSA activity during a head extension maneuver for laryngoscopy which abated after placing the head in a neutral position. This individual had a history of vertebrobasilar artery insufficiency. In Case 6 there was a marked decrease in the EEG-CSA activity of the right hemisphere after acritic unclamping and coming off by pass that persisted till the end of the procedure. The patient developed a left paraparesis that cleared after three days.

Discussion: While only one of six cases showed a direct impact of the EEG-CSA findings on outcome, the five others reported indicate the sensitive versatility of this monitoring mode to alert the Anesthesiologist and Surgeon as to the potential harbingers of cerebral ischemia. Conversely, the EEG-CSA can also demonstrate that an intracranial insult probably did not occur as was noted in Case 1, where CPR was obviously effective in perfusing brain for a period of 30 minutes as was also demonstrated by the good outcome. Head positioning (Cases 3 and 5), may be an occult cause of cerebral ischemia, especially with the older age groups being candidates for these extracorporeal procedures. Flexion, extension, and rotation of the head may cause vertebral artery compression secondary to impingement by the bony canal and osteophytes, by atlantoaxial subluxation, or by constriction by the longus colli and scalenus muscles. Cadaver studies have shown that when the head is turned 60°, flow diminishes in the contralateral vertebral artery and ceases altogether at about 80°. Anesthetic agents and adjuvants in themselves may impact upon cerebrovascular dynamics as can be noted by the seizure activity. Enflurane, having epileptogenic properties, may produce unwitnessed occult seizures under these conditions. Embolization of cholesterol can occur during aortic cross-clamping and air emboli may be released by imprope

CASE	AGE	PROCE.	EVENT	EFG-CSA	OUTCOME
1.	54	CARG	V-Fib and CFR	No Change	Good
2.	6)	CARG	Seisure on Induction After Fentanyl	Occ. loss Lt. and Rt. bemispheric activity, seisures on rew MEG	Expired*
3.	66	CEA(Et.) +CABG	On Bypess Head turned to left Head to neutral po- sition	Loss activity Lt. hemisphere. MEG returns	Good
4.	61	CEA(Et.) *CABG	CZA On Bypass Off Bypass	Decrease activity Rt. Improved activity Rt. Decrease activity Rt.	Good
5.	59	CABO	Read Extension during intubation	Marked decrease Activity left Basilar Wart. Pynd.	Good
٠.	63	FVR	Off Sypans Air?	Marked decrease Activity Rt. hemisph.	Lt.Hemiperesis 72 hours to clear.





itle: ithors: EVALUATION OF THE ACCURACY OF FOUR PULSE OXIMETERS DURING OUTPATIENT DENTAL ANESTHESIA

JA Anderson DDS, MD, ER Kafer, MD ffiliation:

Department of Anesthesiology, School of Medicine, Department of Oral and Maxillofacial Surgery.

School of Dentistry University of North Carolina at Chapel Hill, Chapel Hill 27514

ntroduction.

Outpatient general anesthesia for oral surgery resents a unique challenge for respiratory monioring. Patients are often not intubated and comonly experience periods of hyper- and hypoven-ilation. Airway obstruction, apnea, and laryn-ospasm, may occur easily and patients often move d vocalize during surgery. Since hyoxemia is the rimary cause of morbidity and mortality during nesthesia, an accurate, continuous, and noninvasive unitor of oxygenation is critical.

Pulse oximetry has been shown to be accurate ider steady state conditions. Pulse oximetry has en reported to be useful during dental anesthesia. it accuracy under these rigorous conditions (nonleady state) has not been assessed. The purpose of is study was to assess the accuracy of pulse oxietry during outpatient general anesthesia for oral ingery. We evaluated and compared the accuracy of our pulse oximeters available at the time of begining the study. The oximeters evaluated were the ellor N-100 (Nellor Inc., Hayward, CA), the meda 3700 (Ohmeda, Boulder, CO), the Novametrix odel 500 (Novametrix Medical Systems, Wallingford, Co., Chief March 1988) (Bird 4400 portable pulse oximeter (Bird oducts Corp., Palm Springs, CA).

ethods.

Twenty ASA I and II patients who required reval of third molars and who desired general mesthesia were selected (age: $25.4 \pm SD 8.7 \text{ yrs.}$). 1 institutionally approved informed consent was stained for each patient. Patients received sedaion with midazolam (2.5-5mg) and fentanyl (0.05-.lmg) by i.v. titration. A radial artery catheter is then placed. The finger probes for the four ilse oximeters were then placed in a random fashion 1 the fingers of the hand containing the arterial ine and shielded from each other with gauze. A iseline (sedated) arterial blood sample was then rawn, followed by placement of a nasal oxygen hood, nd 100% oxygen administered. A second blood sample is obtained using methohexital (1-1.5mg/kg) and mintained with intermittent boluses of 10-30mg as Nitrous oxide in oxygen (30-50%) was eded. ministered initially. Arterial blood samples were stained for analysis of measured hemoglobin saturcion by a IL282 CO-Oximeter at 5 minute intervals rring anesthesia and any time a desaturation of reater than 5% occurred. In an attempt to avoid staining samples which were all in the hyperoxic inge, the nasal oxygen hood was removed at a point semed to be the half way point in the surgery and ne patient allowed to breathe room air. Any time ignificant arterial desaturation occurred and peristed for more than a few seconds, oxygen was iministered.

A total of 122 arterial blood samples were obsined over a range of observed SaO, of 70-100%. Imples were analyzed with an IL282 CO-Oximeter for easured saturation (SaO,), carboxyhemoglobin, etheglobin, and total hemoglobin. Methemoglobin anged from 0.0-0.7%. Carboxyhemoglobin ranged from

0.1-6.2% (four smokers were included). To determine the accuracy for each pulse oximeter, the observed $\frac{1}{2} \left(\frac{1}{2} \right) \left(\frac{1}{2} \left(\frac{1}{2} \right) \left(\frac$ SaO₂ values were used as the dependent variable (y) and compared to the in-vitro measured SaO₂ (CO-Ox) as the independent variable (x), and expressed as the least squared linear regression.

The Bird 4400 portable pulse oximeter proved to be the most accurate as it reliably predicted arterial saturation under these conditions (y=1.03x2.8, r=0.85). The Novametrix model 500 and Nellcor N-100 pulse oximeters also demonstrated a high degree of accuracy by linear regression analysis (y=0.97x +2.8, r=0.80) and (y=1.05x -4.1, r=0.84) respectively. In contrast, regression analysis of the observed saturations obtained with the Ohmeda 3700 pulse oximeter revealed that this unit significantly underestimated arterial saturation (y=1.20x - 19.6,

Discussion.

Accuracy is best evaluated by examining the values of the slope and y intercept in the line equation obtained by least squared linear regression analysis. Perfect accuracy would be indicated by a slope of 1.0 and a y intercept of 0. Also, the equation can be used to calculate how well a unit equation can be used to calculate how well a unit would predict SaO₂ (y value) for a given x (SaO₂). When our data are used for an SaO₂ (x) of 50%, the Bird unit underestimated SaO₂ by 1.3% (48.7%), the Nellcor unit by 1.6% (48.4%), the Novametrix unit overestimated SaO₂ by 1.3% (51.3%), and the Ohmeda 3700 underestimated the SaO₂ by 9.6% (40.4%). If 3-4% is considered a significant error in estimating anterial saturation, the Ohmeda 3700 pulse oximeter arterial saturation, the Ohmeda 3700 pulse oximeter is the only unit that produces significant error at 50% Sa0,.

Previous studies have reported accuracy of the Nellcor N-100 under steady state conditions with a high correlation coefficient (y=1.21x - 19.1, r=0.98). A recent study of the accuracy of the Ohmeda 3700 with the version J software (the unit we tested) reported that the unit significantly underestimated arterial saturation under steady state conditions (y=1.21x - 19.1, r=0.98). The correlation coefficient indicates how closely the data points fall around the regression line ("data spread"). It is not surprising that the correlation coefficients obtained in this study during outpatient anesthesia for oral surgery are lower than those reported under steady state conditions.

This study demonstrates that despite the rigorous conditions imposed by outpatient general anesthesia for oral surgery, the Nellcor, Bird, and Novametrix pulse oximeters tested were all linearly accurate in predicting arterial oxygen saturation over the range of 70-100%. The Ohmeda 3700 pulse oximeter was found to significantly underestimate arterial saturation.

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ANESTHETIC IMPLICATIONS IN THE PARTURIENT EPILEPTIC PATIENT

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Introduction. Epilepsy brings about certain problems in the parturient patient however, the complications of this disease as far as the anesthetic management have not been defined. In an attempt to scrutinize the factors determining anesthesia related complications, a retrospective review of epilepic parturient patients requiring anesthesia was done.

Methods. The medical records of 100 obstetric patients with a diagnosis of epilepsy, who were admitted for delivery and/or tubal ligation at Magee Women's Hospital, between 1972 and 1981 were reviewed. The diagnosis of epilepsy was made by the neurology service after conducting clinical examinations and laboratory tests. Factors such as age, gravida, parity, gestational age, abortion rate, type of surgery, type of anesthesia and Apgar scores were examined 1. The results were analyzed for any degree of statistical significance.

Results. The mean age of the patients was 26.17 (S.D.+6.54). Their gravidity was 2.658 $(S.D.+0.17\overline{31})$ and the mean abortion rate was 1,354 (S.D. + 0.114) for a total number of 119 abortions (some patients had more than one abortion). The mean gestational age was 39.213 (S.D.+ 0.272) weeks; 74 patients had vaginal delivery, 13 patients had caesarean sections, 13 other patients had tubal ligations and D&C. Nineteen patients received general anesthesia, 48 patients had spinal anesthesia, 19 other patients received epidural anesthesia and 2 others had caudal blocks, while 12 patients delivered with pudendal blocks. The Apgar score in 77 cases was 8-10 and in 10 cases 4-7. The mean weight of the babies was 3.282 (S.D.+ 57.73)kg. Thirty five patients were taking a combination of phenobarbital and phenytoin, 15 patients received carbamazepine, clonazepam, ethosuximide, acetazolamide, valporic acid and mephobarbital, 15 patients were taking primidone. Thirty five patients were not on any anticonvulsants during pregnancy. Seizures were observed in five patients during the post partum period (table 1). One patient who had enflurane anesthesia developed focal seizures on the third post partum day. Four patients had seizures after spinal anesthesia (two in R.R. and two on the second post partum day). No seizures occurred in patients who had either epidural or caudal anesthesia. Ten patients had babies with congenital malformations,

including two fetal demises (table 2).

Discussion. The major concerns in the pregnant epileptic are loss of seizure control and the possible teratogenic effects of anti epileptic drugs on the fetus 2. During pregnancy, the requirements of anticonvulsant drug therapy change such that strictor control of epilepsy is important in decreasing the incidence of morbidity. Since most of the convulsions occurred in patients receiving spinal anesthesia (8%), it remains to be determined whether alteration of CSF dynamics may favor the eventual occurrence of seizures in epileptic patients. The absence of seizures in patients receiving epidural blocks suggest that this form of anes-

thesia should not be denied to the pregnant epileptic patient, provided the seizure disorder is under control. The incidence of congenital malformations seen in these patient's infants was 11.5%. Five were major; of these three were associated with uncontrolled epilepsy during pregnancy. This incidence of congenital malformations is almost twice the rate of malformations noted in the general population. Epileptic women undoubtedly constitute a high risk group in need of special attention during pregnancy and special care during labor and delivery. References.

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TABLE 1

		DATA ON PATIENTS	THAT CONVULSED	l	
AGE	H/ EPILEPSY	MEDICATION DURING PREG.	PROCEDURE	TYPE OF SEIZURE & TIME OF OCCUR.	ANES.
27	4 MONTHS	VALPROIC ACID 250 MG BID	POST PARTUM TUBAL LIG.	FOCAL SEIZURE	G.A.
25	12 YEARS	P 60 MG BID D 200MG BID M 250MG BID	REPEAT C-SECTION	PSYCHO-MOTOR & PETITMAL POST PAR. II DAY	SPINAL
26	9 YEARS	P 30 MG	VAG. DEL.	GRAND MAL. RECOV. RM.	SPINAL
25	9 YEARS	P 60 MG	VAG. DEL.	POST PARTUM GRAND MAL. RECOV. RM.	SPINAL
36	20 YEARS	NO MEDS.	VAG. DEL.	P.P. GRAND MAL. 2 DAY	SPINAL

TABLE 2

			TABLE 2			
		MATERNAL	AGE AT ONSET	MEDICATION		APCAR
SEX	DEFECT	AGE	OF EPILEPSY	TO MOTHER	OBSERVATION	SCORES
F	ABSENCE OF 1ST TOE RT. FOOT	22	10	P 120MG + 60 D 100MG TID M 250MG BID	BREECH FETAL DISTR C-SECTION	7-9 -
H	CLOSING PDA HEART MURMUR	32	11	CARBAMAZEPINE TID	BREECH	8-9
×	SHORT FRENUM TONGUE	21	9	PIG	PILONOIDAL SINUS	8-9
H	BIL CLEFT LIP & BIL. CLEFT PALATE	27	20	D 100 M 250 BID	APGAR 9-9	8-9
M	CHF AORTIC ATRESIA PDA INOPERABLE	28	22 CAR	P 30 TID D 100 TID BAMAZEPINE 400 UNCONTROLLED EPILEPSY	FETAL DEATH 4TH DAY	6-8
F	FRANK BREECE ABNORMAL FASCIES WEBBED NECK MICRO CEPHALY APGAR 5-7	33	12	ACETAZOLAMIDE ETHOSUXIMIDE UNCONTROLLED EPILEPSY	PREMATURITY MILD RDS FETAL DISTR POST-OP C-SECTION SIDS	5-7
F	MILD MICRO CEPHALY	29	12	PRIMIDONE UNCONTROLLED EPILEPSY	HEART MURMUM PREMATURITY WITHDRAWAL 4TH DAY	8-9
Ħ	BIL. SKIN TAGS ON LITTLE FINGE	31 R	28	-	-	8-9
H	MENINGO HYELOCOELE CONGENITAL HYDROCEPHALOUS BIL. CLUB FEET	36	16	<i>:</i>	-	4-8

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PRESERVATION OF RENAL BLOOD FLOV DURING CONTROLLED HYPOTENSION WITH

FENOLDOPAM IN DOGS

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INTRODUCTION The dopamine 1(DA1) receptor agonist, enoldopam (FDF), decreases systemic blood pressure and necreases renal blood flow and sodium excretion in humans and experimental animals. ^{1,2} The natriuresis induced by FDP suggests that it might play a unique role for deliberate sypotension during general anesthesia. We investigated the semodynamic and renal vascular effects of FDP and sodium sitroprusside (SNP) induced hypotension in dogs receiving allothane general anesthesia.

<u>METHODS</u> Eight adult unpremedicated male mongrel dogs weighing 10-25 kg were studied. Anesthesia was induced using ntravenous surital 15-25 mg/kg. Endotracheal intubation was performed and anesthesia was maintained with 1% end tidal nalothane, 60% N₂O and 40% O₂. The animals were ventilated with an Air Shields Anesthesia Ventilator. End tidal CO2 Engstrom Emma) and end tidal halothane (Puritan-Bennett End Tidal Agent Analyzer) were maintained at 35 mmHg - 40 mmHg and 0.8 - 1.0%, respectively. The left carotid artery was annulated and the systolic and diastolic blood pressure were ecorded on a continuous strip recorder. A Swan-Ganz catheter was positioned in the pulmonary artery. Pulmonary capillary wedge pressure (PCWP) was maintained at 8-12 mmHg with nfusion of 0.9% normal saline through a large bore peripheral ntravenous catheter. EKG and pulmonary artery blood emperature were monitored; the latter was maintained at 36 37°C using humidified gases and a heating blanket. Through a lank incision, an electromagnetic pulse doppler flow probe was secured around the left renal artery with care to avoid vessel constriction. Thirty minutes after completion of the surgical preparation, baseline measurements were obtained. The dogs were randomly grouped to receive either FDP followed by SNP or vice versa. After steady-state conditions were achieved, FDP or SNP was administered via infusion to produce a mean arterial pressure (MAP) of 60 mmHg for 15 minutes. The infusion was urned off and steady state parameters were established again ifter 15 minutes. Next, the remaining drug was infused until a MAP of 60 mmHg was again achieved, and then maintained for 15 minutes under otherwise identical conditions. The infusion was then discontinued, and baseline parameters were eestablished. This sequence was repeated again for both SNP md FDP infusions in each dog. Renal blood flow (RBF), heart ate (HR), systolic and diastolic arterial blood pressure (SBP md DBP), cardiac output (CO), and PCWP were recorded at each baseline state as well as after infusion of both SNP and FDP. MAP was calculated as 1/3(SBP-DBP)+DBP and renal vascular resistance(RVR) as RBF/MAP. For each variable, the sercent change from baseline was calculated and the absolute values recorded for infusion of both SNP and FNP. Values for 3NP vs FDP were compared using a paired T-test with p<.05 onsidered statistically significant.

RESULTS Baseline MAP approximated 95±11 mmHg. Hypotension was easily obtained in all eight dogs using both SNP or FDP. The absolute values for MAP; 69±5 (FDP) and 61±3 (SNP) mmHg were not significantly different. This represented a percent change from baseline of 29±8% and 34±5%, respectively (NS). RBF decreased 15±26% compared to baseline for SNP and increased 15±22% for FDP. This difference was statistically significant (p<.01). DBP decreased 34±11% for FDP and 45±6% for SNP (p<.05).

<u>DISCUSSION</u> Fenoldopam causes vasodilation in renal, cerebral, coronary, and mesenteric circulations. Our data show that FDP produces an increase in RBF during induced hypotension while SNP fails to do so at similar levels of MAP. A major concern when employing controlled hypotension during general anesthesia is the preservation of end organ perfusion and function. The results of this study indicate that FDP has some unique advantages which may well be useful clinically.

% Δ BASELINE

Nitroprusside	Fenoldopam
(SNP)	(FDP)
-3.5 ± 5	-2.6 ± 6
-21 ± 5	-20 ± 6
-45 ± 6	-34 ±11*
-34 ± 5	-29 ± 8
8 ± 16	11 ± 20
-15 ± 26	$15 \pm 22^{\dagger}$
-2 ± 61	-27 ± 27
-5 ± 7	-12 ± 7
	(SNP) -3.5 ± 5 -21 ± 5 -45 ± 6 -34 ± 5 8 ± 16 -15 ± 26 -2 ± 61

^{*} p<.05

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[†] p<.01 vs. value for SNP

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ALFENTANIL AND SUFENTANIL PREVENT THE INCREASE IN 10P FROM SUCCINYLDICHOLINE Title:

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Introduction. Succinyldicholine (SDC) administered intravenously in man increases intraocular pressure (IOP), probably in part by contracture of extraocular muscles and the increase in blood flow in choroidal blood vessels (1,2). It has been demonstrated that prior administration of a subparalysing dose of non-depolarizing muscle relaxants (3,4), lidocaine (4), diazepam (5) and deep anesthesia prevent an increase in IOP from SDC. However, some studies have failed to confirm the efficacy of these approaches (2) and therefore the use of SDC in patients with open eye injuries has been generally considered to be contraindicated. Alfentanil (ALF) and Sufentanil (SUF) have been shown to block the cardiovascular responses to laryngoscopy and intubation (6). Since these maneuvers potentiate the rise in IOP following SDC (2), the purpose of this study was to examine the efficacy of these agents with DTC defasciculation in preventing the rise in IOP following SDC, laryngoscopy and intubation.

Methods. This study was approved by the Hospital Human Investigation Committee and informed consent was obtained. Thirty patients (ASA Class I and II) weighing 40-109 kg, scheduled for elective non-ocular surgery, were divided into 3 groups of 10 (Table). IOP was measured with a Mueller's electronic tonometer using a weight of 5.5 g. Heart rate and blood pressure were recorded at each measurement of IOP. All patients were preoxygenated with a face mask. Measurements were made prior to drug administration (a) and 20 mins following premedication (b)(II, III), 3 mins following DTC administration (c), 15 sec following thiopental (d)(I, II), 20 sec (I, II, III) and 40 sec (I, II) following SDC administration (e,f) and at 15, 60, and 120-180 seconds following endotracheal intubation (g,h,i)(Figure). Patients were ventilated manually with 100% 02 between measure-TABLE ments.

	PREMEDI-		INDUCTION	MUSCLE
GROUP	CATIONS	DEFASCICULANT	AGENT	RELAXANT
I		DTC 0.06*	THIO 5*	SDC 2*
II	SUF .05 ⁺	DTC 0.06*	THIO 7*	SDC 2*
III	MID 0.025	* DTC 0.06*	ALF 150 ⁺	SDC 2*

+ doses given mcg/kg IV; * doses given mg/kg IV Data were analyzed by ANOVA with I repeated measure. A p<0.05 was considered statistically significant.

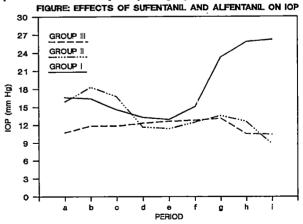
Results. Patients were comparable in terms of age, weight, and physical status. Baseline IOP was similar for all groups (Figure). Group I: IOP, BP and HR did not change significantly following DTC, THIO or SDC. However, laryngoscopy and intubation resulted in significant increases in IOP, BP and HR. Group II: IOP, BP and HR did not change significantly following SUF, DTC and THIO. Furthermore, they remained unchanged following SDC and did not increase after laryngoscopy and intubation. Group III: IOP did not change 20 min after SUF and MID, 3 min after DTC, 20 sec following ALF

and SDC, and after laryngoscopy and intubation. BP and HR did not change during intubation as well.

Intubating conditions were considered to be very satisfactory in all groups. Fasciculations, bucking or coughing were not observed in any patients. One patient in Group III complained postoperatively of pruritis which was treated satisfactorily with diphenhydramine hydrochloride.

Discussion. The results of this study are in agreement with previous reports that SDC following induction with THIO increases intraocular pressure and that a subparalyzing dose of DTC (2,4) does not prevent this increase. More importantly, we have shown that additional pretreatment with a subanesthetic dose of SUF (with or without midazolam) and/or induction with ALF effectively prevented increase in intraocular pressure following SDC and intubation. Since stress response to intubation may cause a greater increase in IOP than from SDC, the beneficial effect of a short-acting narcotic in preventing increase in IOP is not entirely unexpected. Although the induction dose of THIO was higher in Group II than in Group I we have previously demonstrated that this alone is not likely to have been responsible for the effect seen on the IOP (7).

In conclusion, we have shown that SUF premedication and DTC pretreatment plus high dose THIO or ALF induction effectively blocked the increase in IOP from SDC and intubation. Since SDC is an invaluable muscle relaxant for rapid sequence endotracheal intubation, these results may have a far reaching effect in anesthetic management of patients with an open-eye injury (8).



See Methods for discussion of time periods. Data means are presented graphically. References:

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CENTRAL RESPIRATORY EFFECTS OF PROPRANCIOL AFTER ACUTE IV ADMINISTRATION

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are Introduction. Beta-adrenergic blocking drugs are frequently used to treat ischemic cardiac disease and hypertension. Beta-blockers may also have significant respiratory effects. Although bronchospasm is a well known complication of these drugs, it is unclear whether or not central respiratory depression can also occur. Answers to this question have been conflicting, at least in part. because most often only the ventilatory response to CO₂ ($\mathring{\mathbf{V}}_{E}$ vs CO₂) and not the occlusion pressure response (P_{O-1} vs CO₂) has been examined. $\mathring{\mathbf{V}}_{E}$ vs CO₂ could be decreased by either central respirator depression or increased airway resistance whereas P_{0.1} vs CO₂ should only be affected by centra-respiratory depression. In addition, all studies to date examined the effects of oral beta-blockers, and not the effects of acute intravenous administration We, therefore, studied 12 volunteers in a doubleblind, randomized crossover fashion to determine i any significant central respiratory depression occurs after intravenous administration of a betablocking dose of propranolol.

Methods. Twelve healthy adult nonsmoking male: with no history of asthma were studied after Institutional Review Board approval. Respiratory drive was assessed by analysis of the slopes of the ventilatory (v_E) and occlusion pressure (P₀₋₁) response to progressive hypercapnea under hyperoxic condi-tions using a modified Read rebreathing circuit. Subjects were NPO for at least 8 hr prior to study. Resting heart rate (HR), systolic blood pressure (SBP), end-tidal CO2 (ETCO₂) and response to CO₂ rebreathing were obtained after placing a 20-gauge plastic IV catheter and beginning an infusion of normal saline at 100 ml per hr. In addition, the HE response during CO rebreathing was documented. After a 15 min rest period, either normal saline or propranolol (0.1 mg/kg) was infused over 10 min in a double-blind manner. HR and SBP were measured every minute during this infusion. 5, 30 and 60 min after finishing the infusion, additional CO challenges were performed in the same manner as the baseline test. Subjects returned no sooner than 48 hr later to receive the crossover drug and be evaluated in the same fashion. We examined HR and SBP changes during the 10 min infusions as well as during CO₂ rebreathing to determine if beta-blockade had beer achieved. The slopes of V_E vs CO₂ and P_O vs CO₂ were compared between groups (propranolol vs NS) to determine if any respiratory depression occurred. Hotelling T-square, chi-square, and paired and unpaired t tests were used. P values < 0.05 were considered statistically significant.

Results. During the propranolol infusion HRs decreased significantly (from 65 to 56) while they did not during NS (from 60 to 59). In addition, while maximum mean HR's during CO rebreathing were similar at both baseline sessions, subjects receiving propranolol had significantly slower maximum HRs

during CO₂ rebreathing when compared to NS at all test times (Table 1). Propranolol did not produce any statistically significant changes in the resting ETCO₂ or the ventilatory or occlusion pressure response to CO₂ when compared to baseline or NS (Table 2, 3, 4).

Table 1. Maximum Mean HR (BPM) During CO₂ Rebreathing Before and Min After Infusion of Either Propranolol or NS.

	0	5'	30'	60 '
Propranolol	87	71 *	73 **	73**
NS	84	86	82	81

*P < 0.05 compared to NS; **P < 0.005 compared to NS

Table 2. Resting ETCO₂ (mmHg) Before and Min After Infusion.

	0	5'	30'	60'
Propranolol	34	35	35	34
NS	34	34	34	35

Table 3. Slope of \dot{V}_E vs CO₂ (L/min/mmHg) Before and Min After Infusion.

	0	5'	301	60'
Propranolol	3.87	3.32	3.25	3.45
NS	3.64	3.21	3.58	3.17

 $\frac{{\rm Table}\ 4}{{\rm and\ Min}}$ Slope of P $_{0\ \cdot\cdot\,1}$ vs CO $_{2}$ (cmH $_{2}{\rm O/mmHg})$ Before and Min After Infusion.

	0	5'	30 '	60'
Propranolol	1.06	1.05	1.07	1.07
NS	1.12	0.92	1.11	1.07

Discussion. These data demonstrate that the acute administration of beta-blocking doses of propranolol does not produce significant central respiratory depression, in healthy adult volunteers. We also found no decrease in the ventilatory response to CO₂ indicating little, if any, change in airway resistance after propranolol. Although synergism may exist when combined with other drugs, beta-blocking doses of IV propranolol alone appear devoid of respiratory effects in healthy adults.

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Introduction. A recent NIH Consensus Development Conference reported a marked increase nationwide in Fresh Frozen Plasma (FFP) administration in the absence of proven clinical efficacy (1). Subsequent to that report we examined justifications for transfusing FFP in the perioperative period (2). We now report a study evaluating the impact of a controlled program of medical education on physician compliance with recommended indications for FFP therapy.

Methods. Patients receiving perioperative transfusions of FFP at Temple University Hospital, between Dec 1985 and Mar 1986 (Group A, control), and between Dec 1986 and Mar 1987 (Group B, post-intervention), inclusive, were identified by the blood bank. The charts and anesthesia records were reviewed by the authors, within 48 h of surgery. Information sought included type of surgical procedure, estimated blood loss, blood products given, liver and renal function, hematologic profile, and administration of drugs known to alter coagulation. The authors also interviewed the staff and resident anesthesiologist regarding justification for using FFP. A questionnaire classified their response into 1 of 6 categories. Untoward bleeding and presumption of coagulopathy was based on the staff anesthesiologist's assessment of the situation. Documentation of coagulopathy was based on the preoperative coagulation profile.

Tuctifications Authors
Justifications Authors
for use of FFP Assessment
1.) Surgeon insists - no untoward bleeding NI
2.) Hypovolemia NI
3.) Presumed coagulopathy - no untoward bleeding NI
4.) Presumed coagulopathy & untoward bleeding PI
5.) Documented coagulopathy - no untoward bleeding PI

A definite indication (I) for transfusion of FFP was documented coagulopathy with untoward bleeding. Possible indications (PI) were defined as presumed coagulopathy with untoward bleeding, and documented coagulopathy without untoward bleeding. A designation of not indicated (NI) was assigned to hypovolemia, surgeon insistence or a presumed coagulopathy in the absence of untoward bleeding.

6.) Documented coagulopathy & untoward bleeding

The formal educational effort consisted of lectures presented at grand rounds in the departments of Anesthesia, Surgery and Internal Medicine. A follow-up questionnaire distributed to all faculty and house staff in the above specialties reinforced lecture data. Informal small group discussions and the usual staff-resident interaction in the operating room and on teaching rounds in the SICU were utilized. All teaching was done by the authors and took place between Mar 31 and Dec 1 1986. Statistical significance was determined with the chi square test and the Fisher exact test.

Results. The total number of operative cases during the first time period was 2077 and during the second .2540.

In group A (n=32) nineteen patients had cardiac surgery, in group B (n=18) eleven patients had cardiac surgery. The remainder in each group had general and subspecialty surgeries. Comparison of the patients in each group to the 6 justifications is seen in Table 2.

	Table 2	
Justifications	Number of	Patients
	Group A	Group B
l (NI)	10	3
2 (NI)	2	1
3 (NI)	5	0
4 (PI)	6	11
5 (PI)	2	0
6 (I)	7	3

Fifteen (47%) of the patients in group A received FFP for what we considered a definite or possible indication. Seventeen (53%) received FFP based on indications we considered inappropriate. In group B, 14 (78%) of the patients received FFP for what was considered a definite or possible indication. Four (22%) received FFP based on indications considered inappropriate (Table 3).

		Tab.	le <u>3</u>	
Grou	p Total	FFP .	Appropriate	Inappropriate
•	OR cases	recipients	Use (I,PI)	Use (NI)
Α	2077	32(1.54%)	15(47%)	17(53%)
В	2540	18(0.71%)	14(78%)	4(22%)

Statistical analysis of the data revealed that the decrease in the number of patients transfused FFP, from 32 of 2077 operative cases in group A to 18 of 2540 operative cases in group B, was significant (p<0.01). Analysis of the indications for transfusion of FFP revealed that the decrease in unacceptable justifications, from 53% in group A to 22% in group B, and conversely the increase in acceptable justifications from 47% to 78% was also significant (p<0.05).

<u>Discussion</u>. Despite an increase in the number of operative cases during the second time period there was a statistically significant decrease, in the number of patients given FFP, and in the unacceptable justifications for transfusion of FFP. Although it is difficult to quantitiate the informal teaching that accompanied the lectures and follow-up questionnaires, it is clear that the program had a positive impact on physician performance.

In view of the inherent risks and costs involved in the transfusion of blood products, and the results of this study, we believe efforts aimed at re-education of physicians regarding indications for and actions of FFP should continue.

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ONSET, DURATION AND REVERSAL OF PIPECLRONIUM INDUCED NEUROMUSCULAR BLOCKADE UNDER BALANCED

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Introduction: Pipecuronium bromide (PIP) is a nonlepolarizing muscle relaxant similar to pancuronlum but reported to have minimal cardiovascular side effects (i). The $\mathtt{ED_{90}}$ of PIP has been determined to be approximately 35 µg/kg in young and middle aged people (1). The purpose of this study as to evaluate the neuromuscular parameters of 'IP in patients anesthetized with a balanced anes-:hesia. We investigated the onset, duration, reovery from neuromuscular blockade and intubation onditions following doses of two to three times he EDgo of PIP.

lethods: Ten male and 20 female patients (ASA lass I=III) ages 22=63 years old weighing 48=100 ig gave their written informed consent to particiate in this institutional review board approved itudy. Subjects were randomly assigned to receive ither 70 (n=10), 85 (n=10) or 100 (n=10) μ g/kg of IP. After premedication with morphine (0.1 (g/kg) and atropine (0.4 mg) IM, anesthesia was nduced with fentanyl (3-6 µg/kg)and thiopental 3 = 6 mg/kg) and $N_2 O/O_2$ (60/40). Maintenance of nesthesia was with N20/02 with fentanyl or thioental as needed. Dosages of PIP (5+10 µg/kg) ere also given to maintain neuromuscular blockade. fter induction, the isometric force of contracion of the adductor pollicis muscle was elicited tilizing a train-of-four(TOF) at 2 Hz supramaxial square wave impulse of 0.2 msec duration every 2 sec via surface elecrodes over the ulnar nerve. IP was administered as a single bolus over 5 sec. ntubation was attempted within 1 min after compleion of neuromuscular blockade, and relaxation was cored on a scale of 1-4, where 1 was flaccidity nd 4 was vigorous resistance to intubation. The ime to 90% block of the first twitch of TOF (T_1) , aximum T₁ block, time to maximum T₁ block and ime to 5, 10 and 25 percent of T_1 recovery were ompared between the 3 groups. When the neuromusclar block was no longer required, the residual lock was reversed with neostigmine (2.5mg) and lycopyrrolate (0.5 mg). Recovery of T_1 compared

ita is presented as means ± S.D. sults: No significant difference in demographic ariables was demonstrated between the groups. immary of neuromuscular data is presented in able 1. While the time to 90% and maximum T_1 lock was longer in the group receiving the lowest ose of PIP, the difference among the three groups id not reach statistical significance. The time om administration of PIP to start, 5; 10 and 25% ecovery of T1 was significantly longer in the roups receiving 85 and 100 µg/kg than in the 70 3/kg group. However, there was no significant ifference between the 85 and 100 µg/kg groups. 1 addition, no significant difference in the time om 5-25% or 10-25% recovery time could be shown mong the groups. No significant differences were

o its baseline value was determined prior to and t 2, 5, 8 and 10 min after reversal administra-

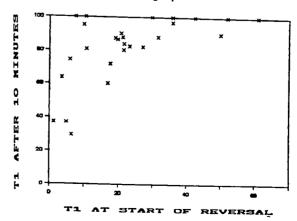
ion. Statistical analysis were performed utilizig one way ANOVA and Kruskal-Wallis test. A p < .05 was considered statistically significant.

seen in intubation scores between the groups. Of the 30 patients, 29 had excellent or good relaxation scores; only one patient (in the 85 µg/kg group) had a poor intubation score. Percent recovery of T_1 obtained prior to and at 2, 5, 8 and 10 min after reversal administration was not different between the groups. Adequate recovery of muscle relaxation following reversal was more dependent on the residual block at the start of reversal (Fig 1). Patients who had recovered to at least 30% baseline T_1 at time of reversal had adequate clinical recovery in less than 10 min, while patients with less than 10% recovery took longer. Discussion. The results of this study confirm that PIP appears to be a relatively fast acting neuromuscular blocker with a long duration of action. Under balanced anesthesia, a 70 µg/kg dose of PIP will provide clinical neuromuscular relaxation for approximately one hour. In our experience, this is comparable to that provided by similar doses of pancuronium. While our study did not demonstrate any differences in intubating conditions between the groups, this was possibly because patients were intubated after maximum block had been reached. Recovery from blockade was successful in all patients, but the time to recovery depended on the amount of residual blockade.

TABLE 1. Neuromuscular and intubating parameters

The state of the s							
Time (min) to	70 µg/kg	85 µg/kg	100 µg/kg				
90% T ₁ block	2.5(0.9)	2.0(0.6)	2.1(0.6)				
Max T ₁ Block	3.6(2.1)	3:5(1:1)	3.0(0.8)				
Onset of T ₁ Recovery	38.2(8.2)a	57.3(15.6)	58.3(15.6)				
5% T ₁ Recovery	50.0(14.1)b	71.9(15.7)	71:8(22:1)				
10% T ₁ Recovery	58.7(18.1)b	82.5(16.4)	74.9(18.0)				
25% T ₁ Recovery	66.7(14.0)b	98.3(18.7)	94.6(18.0)				
5% to 25% Recovery	22.6(6.1)	27.4(6.1)	28.8(8.1)				
10% to 25% Recovery	14.7(4.7)	17:3(3:8)	19.2(6.5)				
Intubation Score	1.3(0.5)	1.6(0.7)	1.4(0.5)				
a p < 0.01 as compared	to other gro		1.7(0.5)				

bp < 0.03 as compared to other groups



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Title: BW A938U PHARMACOKINETICS AND DYNAMICS IN HEALTHY SURGICAL PATIENTS UNDER ISOFLURANE ANESTHESIA

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Introduction: BW A938U is a new benzylisoquiniline nondepolarizing neuromuscular blocking agent currently undergoing multicenter clinical trials. It has a long duration, is devoid of cardiovascular effects and is readily reversible with anticholinest erase agents. This is the first study designed to define the pharmacokinetic profile of BW A938U following a single intravenous injection in patients under N20/02/isoflurane anesthesia.

Methods: After obtaining IRB approved written informed consent, 24 patients (18-50 years old, ASA class I-II) were studied. No patient with a history of malignant hyperthermia, drug abuse, neuromuscular, neurologic, psychiatric, cardiac, renal, or hepatic disease was studied. Nor were patients exposed to steroids, phenytoins, barbiturates, or antihistamines. Patients were premedicated with diazepam (5-15mg po) and morphine (5-10 mg IM). Anesthesia was induced with thiopental (4 mg/kg) and fentanyl (2-4 ug/kg) IV. The trachea was intubated under isoflurane without the use of relaxants. After intubation end tidal isoflurane concentration was adjusted to and maintained at 0.8% in 60% N₂0 and 0₂. Blood pressure, EKG, 0₂-saturation, end-tidal CO₂, and temperature were monitored and recorded. All patients were normoventilated and temperature maintained between 35-37°C. The evoked mechanical response of the ulnar nerve-adductor pollicis system was monitored using supramaximal square wave impulses at 0.15Hz via steel needle electrodes at the wrist. Following stabilization of the twitch response and 15 minutes of stable end-tidal isoflurane at 0.8%, a single rapid IV injection of BW A938 was given over 5 seconds. Blood pressure was monitored every minute for the first ten minutes and every five minutes thereafter. Blood samples for determination of plasma concentration of BW A938U were drawn from a separate large bore sampling catheter at 0,2,5,10,20,30,45,60,90,120,180,240 360 and minutes. Urine was collected from 12 patients via an indwelling foley catheter for 12 hours to measure recovered BW A938U and any metabolites. Samples were analyzed by an HPLC method and the data fitted to both two-and three-compartment pharmacokinetic equations. Three dose groups were studied with eight patients per group (A:25 mcg/kg, ED95; B:50 mcg/kg,2xED95; C:80 mcg/kg, 3xED95). Pharmacodynamic data was analyzed by group t-test with p40.05 considered significant.

Results: The pharmacodynamic data is complete on all patients. Pharmacokinetic data analysis is complete on ten patients. Best fit was achieved with a three-compartment model. The data is summarized in tables I and II. No effects on heart rate or blood pressure following BW A938U bolus was seen in any patient, nor were signs of histamine release. In the six urine samples currently analyzed, 25.3 to 46.4 per cent of the injected dose of BW A938U was recovered in the first twelve hours, predominantly unchanged.

TABLE I BW A938U PHARMACODYNAMICS

	Grp_A(n=8)	Grp B(n=8)	Grp C(n=8)
Max Block	96.6 <u>+</u> 1.9	100(99.6)	100(100)
Onset (min)	7.7 <u>+</u> 1.03	4.19±0.27(5.3)	4.04±0.75(3.4)
Begin Recovery (min)	40.5 <u>+</u> 9.0	60.6±9.5(49.8)	98.7±25.9(124.7)
Dur 5 (min)	54.8 <u>+</u> 9.2	71.0±9.7(57.9)	114.1±28.1(134.6)
Dur 25 (min)	67.5 <u>+</u> 8.9	90.4±16.4(82.9)	169±36.9(158)

all values <u>+</u> SE () Ref. 1; N₂O/O₂/Narcotic anesthesia; p¹₂O.05

TABLE II BW A938U PHARMACOKINETICS

	Grp A(n=4)	Grp B(n=3)	Grp C/kg(n=3)
t 1/2 8 (min) t 1/2 α (min) t 1/2 β (min) VC (ml/kg) Vdss (ml/kg) Cl (ml/kg/min) MRT (min)	2.0±0.35	1.5±.12	1.7±.06
	19.2±3.4	15.7±2.1	19.3±4.5
	122.2±21.6	136.5±16.4	150±25.9
	28±5	29±6	44±2
	168±14	190±29	278±38
	1.5±.21	1.4±.023	2.2±.23
	74.1+20.2	100.6±42.5	131.8±10.9

all values +SE

Discussion: This study confirms data from other investigations that BW A938U is a long-acting nondepolarizing relaxant that is without effect on heart rate and blood pressure. Interestingly in this study compared to identical dosage groups under nitrous/narcotic anesthesia, the recovery times under isoflurane tend to be somewhat longer, but did not reach statistical significance. The pharmacokinetic data thus far analyzed indicates BW A938U to behave in a similar fashion to the currently used long-acting agents. Yet to be fully determined is if there is an additional mode of excretion other than via the kidneys, if there is any metabolism/excretion by the liver, if there is significant plasma cholinesterase metabolism in vivo, and if there is pharmacokinetic linearity between dosage groups. Studies to address these issues are also in progress.

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TITLE:

PREPARATION OF ANESTHESIA MACHINES FOR PATIENTS SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

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Introduction. Malignant hyperthermia is a potentially ethal syndrome which can be triggered by inhaled anesthetics. Since an anesthetic concentration low enough not to trigger nalignant hyperthermia has yet to be determined, anesthesiologists may wish to choose equipment that minimizes exposure of susceptible patients to inhaled anesthetics. Some nvestigators recommend that a special anesthesia machine (never exposed to inhaled anesthetics) be reserved for these patients, that it is not practical in many hospitals. Others suggest that a contaminated machine can be used safely if it is flushed with exponent is longer than necessary, we determined the rate at which esidual halothane concentrations decreased in an anesthesia nachine being flushed with oxygen.

Methods. Anesthesia equipment included an Ohio Modulus® machine, an Air Shields® ventilator, and disposable olyethylene circle systems (Marquest®). The equipment was aturated with 2.0% halothane for 18 h by delivering a 1-L/min esh gas flow, plugging the elbow at the end of the circle system, nd setting the tidal volume of the ventilator at 600 ml and the ate at 10 breaths/min. Washout from the anesthesia machine ras evaluated by measuring halothane concentrations in samples aken from the elbow of the circle system under four different onditions: 1) without changing the anesthesia equipment; 2) after hanging the soda lime (Sodasorb®); 3) after changing the soda me, circle system, and fresh gas outlet hose; and 4) aftehanging the soda lime, circle system, fresh gas outlet hose, and entilator bellows. During the washout period, the vaporizer was emoved from the circuit, fresh gas flow was increased to 0 L/min, and the ventilator left on. Halothane concentrations Iso were determined in gas samples taken from the end of the esh gas outlet hose when: 1) the original hose was left in place nd 2) the hose was replaced at the beginning of the washoueriod. Samples were analyzed with a Gowmac® gas chromatograph aving a sensitivity of \approx 0.1 parts per million (PPM).

Results. Halothane concentrations in samples obtained om the elbow were similar with original or fresh soda lime, but ere 10-fold lower after the fresh gas outlet hose and circle istem were replaced. Changing the ventilator bellows did not rither increase the washout rate (Fig. 1). Halothane incentrations in samples taken from the end of the original fresh is outlet hose were similar to the concentrations obtained from elbow after the fresh gas outlet hose and circle system were placed. However, halothane concentrations in the fresh gas flow imples obtained following replacement of the outlet hose were lother 5-fold lower and decreased so rapidly that halothane was 1 PPM after 5 min of washout (Fig. 2).

Discussion. These data suggest that the fresh gas outlet se is a major halothane reservoir, but that soda lime is not. The ntilator also appears to be a reservoir because halothane ncentrations sampled from the elbow after changing the soda le, circle system, and fresh gas outlet hose were 5-fold higher an samples from the end of the new fresh gas hose. Changing the ntilator bellows was not effective, because the Air-Shields® ntilator contains many internal rubber components. Residual esthetic concentrations were lowest in samples collected from fresh gas supply after the outlet hose had been changed. Ilothane concentrations at the end of the new fresh gas hose creased 4 orders of magnitude in 2 min but then required 8 h decrease by another order of magnitude. Halothane ncentrations were less than 1 PPM within 5 min of washout, libelow the National Institute of Occupational Safety and Health

standard for waste gas exposure.³ Consequently, malignant hyperthermia susceptible patients will be exposed to minimal inhaled anesthetic concentrations when a disposable, non-rebreathing circuit is connected to a "contaminated" machine that has been prepared by: 1) removing vaporizers, 2) flushing with oxygen at a rate of 10 L/min for 5 min, and 3) changing the fresh gas outlet hose.

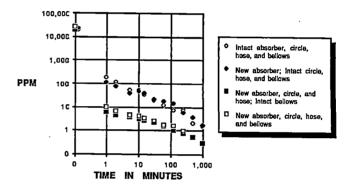


Figure 1: Washout from an anesthesia machine saturated with 2.0% halothane. Gas samples were taken from the elbow of the circle system.

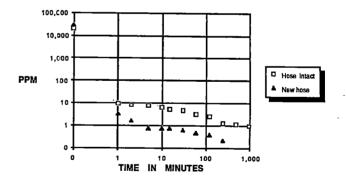


Figure 2: Washout from an anesthesia machine saturated with 2.0% halothane. Gas samples were taken from the end of the fresh gas outlet hose. When the fresh gas outlet hose was changed, the halothane concentration after 5 min of washout was < 1 PPM (i.e.. $\approx 1/10,000$ th MAC).

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Title: CONTINUOUS FLOW APNEIC VENTILATION IN LUNG INJURY INDUCED BY OLEIC ACID INJECTION IN THE DOG

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Introduction: Continuous flow Apneic ventilation (CFAV) produces adequate gas exchange for 5 hours in anesthetized and paralyzed dogs. CFAV is also effective during prolonged thoracotomy in dogs. 2
Tallman et al reported that CFAV may be useful in lung injury induced by intravenous injection of oleic acid (OA). 3 The present study is designed to evaluate cardiovascular effects and gas exchange in dogs with OA-induced lung injury. Ventilation was supported by intermittent positive-pressure ventilation (IPPV) with Positive end-expiratory pressure (PEEP), CFAV with continuous positive airway pressure (CPAP) or CFAV with intermittent madatory ventilation (IMV) and PEEP. Methods: Fifteen dogs (mean wt 20 kg) were anesthetized with thiopental (25 mg·kg⁻¹) followed by an infusion of 4 mg·kg⁻¹·hr.⁻¹ The dogs were intubated with a double-lumen endobronchial tube and ventilated with IPPV, volume and rate adjusted for normocarbia. Fluid status was supported by an infusion (3 ml· kg⁻¹ · hr⁻¹) of a balance salt solution containing 50 meq NaHCO₃ per liter. Paralysis was obtained by bolus injection of vecuronium (0.1 mg · kg⁻¹) and maintained by an infusion of vecuronium (1 µg·kg⁻¹·min⁻¹) monitored by a peripheral nerve stimulator. The femoral artery and vein were cannulated, and a pulmonary artery catheter was placed through an incision in the neck. Two 2.5 mm ID catheters were inserted into the endobronchial tube (one into each lumen) with the tips lying 1.5 cm below the carina. Placement was verified by fiberoscopy. The catheters were sealed during IPPV. CFAV provided by a gas system consisting of an air/oxygen blender, calibrated flow meter, heated humidifier, oxygen analyzer and tubing. All dogs were ventilated with an F_1O_2 of 0.5 during the study. Total flow during CFAV was 1.2 1 kg⁻¹ min⁻¹. Control numbers were recorded after 30 minutes of IPPV or CFAV. The dogs were again ventilated with IPPV and OA (0.05 ml kg 1) was injected into the right atrium. After allowing the model lesion to develop for 1 hour, 5 dogs were maintained with IPPV and PEEP (5 mmHg), 5 dogs were maintained with CFAV and CPAP (adjusted to give the same mean airway pressure (Paw) obtained during IPPV with PEEP), and 5 dogs were maintained with CFAV plus IMV (2 breaths per minute) and PEEP (5 mmHg). Arterial and venous blood gases, cardiovascular values and temperature intervals. Statistical measured at significance was estimated by a two-way analysis of variance followed by the Dunnett t-test. Results: Arterial blood gases are presented in the two tables (mean + SD). Prior to lung injury, CFAV achieved adequate gas exchange in each group of animals. Intra-atrial OA caused the mean arterial oxygen (PaO₂) and mean cardiac index to decrease in each group while the mean arterial carbon dioxide (PaCO2) increased in both CFAV groups and the mean pulmonary venous admixture gradually increased in all three groups of animals. The OA-injured group ventilated with CFAV + IMV + PEEP had a significantly higher (p \leq 0.05) mean PaO₂ at 60

minutes than the group ventilated with CFAV + CPAP, but the OA-injured group ventilated with CFAV + CPAP

had a significantly higher ($p \le 0.05$) mean PaCO₂ at 60 minutes than the group ventilated with either IPPV + PEEP or CFAV + IMV + PEEP.

Discussion: It is known that CFAV is almost as effective as IPPV in the ventilation of dogs with normal lungs. 1 , 2 After OA lung injury, dogs subjected to CFAV + CPAP developed marked respiratory acidosis, but dogs subjected to CFAV + IMV + PEEP only developed mild respiratory acidosis (p < 0.05 at 60 minutes and 120 minutes). We believe that edema fluid resulting from OA injury fills small airways and prevents peripheral distribution of ventilatory gas during CFAV + CPAP. Nevertheless, low-frequency (2 breaths per minute) IMV proved to be effective in CO₂ elimination in this model. CFAV + CPAP failed to produce adequate oxygenation and ventilation in a model of lung injury. However, CFAV + IMV + PEEP was successful in producing both adequate oxygenation and ventilation in this model. References:

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Tables:

PaCO2 (mmHg)

IPPV + PEEP CFAV + CPAP CFAV + IMV + PEEP CONTROL $34.4 \pm 3.0 \ \underline{\text{NS}} \ 37.8 \pm 2.9 \ \underline{\text{NS}} \ 42.0 \pm 2.7$ NS NS 47.2 ± 5.9 NS 40.0 ± 8.6 CONTROL 39.4 ± 7.2 (CFAV) NS 36.8 <u>+</u> 8.3 NS 41.6 ± 4.1 NS 40.6 ± 3.7 OAIPPV NS 60 min 39.0 ± 12.8 <u>S</u> 81.8 ± 20.5 <u>S</u> 45.7 ± 4.0 NS_ 120 min 36.6 ± 13.7 NS 78.4 ± 10.4 S 47.9 ± 5.4

Pa02 (mmHg)

IPPV + PEEP CFAV + CPAP CFAV + IMV + PEEP 188 <u>+</u> 27 <u>NS</u> 197 <u>+</u> 29 <u>NS</u> 249 <u>+</u> 66 CONTROL (IPPV) NS 202 + 52 NS 177 + 43 NS 152 + 26 CONTROL (CFAV) NS 106 ± 27 NS 145 ± 43 NS 188 ± 60 OAIPPV NS 60 min 118 <u>+</u> 42 <u>NS</u> 73 <u>+</u> 15 <u>S</u> 109 <u>+</u> 8 NS 143 ± 59 <u>NS</u> 85 <u>+</u> 29 <u>NS</u> 112 <u>+</u> 18 120 min

itle: ACQUISITION OF AUDITORY INFORMATION DURING DIFFERENT PERIODS OF GENERAL ANESTHESIA.

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Introduction. Amnesia for events under general anesthesia has traditionally been inferred by the lack of postoperative verbal recall for events during surgery. However, several recent studies have shown that acquisition of auditory information during anesthesia can be demonstrated (1, 2, 3). Presentation of experimental information was confined in these studies to one discrete point during the anesthetic: before skin incision (1), just before emergence (2), and during stable surgical anesthesia (3). The present study was designed to test differences in auditory acquisition as a function of the time the patient is under anesthesia and the anesthetic agents administered. A standardized meaningful message will be presented to patients during lifferent phases of clinical anesthesia followed by postoperative interviews which will assess verbal and ionverbal memories of the experimental message.

Methods. Forty-eight patients ASA I-II, aged 19-63 yrs., scheduled for elective surgery were chosen. Each consented to be a participant and institutional approval rom the Human Subjects Review Committee was obtained. Patients were told that surgical personnel often assume that the patient does not record their conversations. The patient was told to listen for a pecial message during anesthesia. To increase the neaningfulness of the neutral study message patients were also told that a personal message for their good ecovery would precede the study message. The nterviewer made a tape recording for each patient which included 1) the patient's preferred name, 2) resonalized statements of well-being regarding the pecific operation, 3) suggestions for recovery, and 4) statement on the importance of engaging in a specific ehavior during a postoperative interview. The behavior was randomly assigned among patients from four hoices: (a) touching the right or (b) left ear, (c) lifting ne left or (d) the right index finger.

ratients requiring general anesthesia for GI, ynecological, orthopaedic, or plastic surgeries were tudied. No attempt was made to control the anesthetic schnique. All patients received nitrous oxide (40-67%) nd isoflurane (.25-1.5%)(n=29), halothane (.5-2%)(n=11), r ethrane (1-3%)(n=8). Anesthetic IV agents included odium thiopental, diazepam, fentanyl, and morphine alphate. The anesthesiologist confirmed that patients ere adequately anesthetized and clinically stable. HR nd BP did not change with presentation of the lessage. All anesthetic agents and their doses related to le time of message delivery were recorded. resentation of the experimental message was via tape excorder through stereo earphones fitted by a separate experimenter and monitored to insure adequate resentation over a separate set of earphones. Ostoperative interviews were conducted 1 to 20 days ostanesthetically. The two interviewers recorded all stances of the four nonverbal target behaviors iroughout the 30 minute interview, at the end of which he entire taped message was played to the patient, reaking the blind condition for the experimenters. The resence or absence in the interview of the specific shavior mentioned in the experimental message was

taken as evidence for or against learning during general anesthesia.

Pre- and intraoperative variables were recorded from patients, anesthesia doses, and presentation of the message. Amounts of medications, induction agents, and anesthetics, the time that the message was played to the patient after induction and before emergence, anesthetics present at that time, pre- and intraoperative hemodynamics, and postoperative interview responses, including nonverbal responses were recorded. A mathematical model (logistic regression) was developed from these data to determine which variables correlated with the presence of the suggested behavior in the postoperative interview.

Results. MESSAGE PRESENTATION: Time of message presentation varied from 15 to 293 minutes after induction (10 to 219 minutes before emergence). The mean time to message presentation was 93 minutes after intubation (st.dev. = 64.3 min.) and 59 minutes before emergence (st.dev. = 58.2 min). EFFECTS OF MESSAGE: Interview questioning revealed that no patient verbally recalled the experimental message or any intraoperative event.

Interview observation of patients' nonverbal behavior revealed responses to the intraoperative message in 33 cases and a lack of a specific response in 15 cases. The statistical model found two variables associated with the postoperative nonverbal behaviors: 1. presentation of the message for that behavior (p<.02), and 2. a nonsignificant trend for intraoperative IV diazepam to suppress the response (p=.13). A noteworthy finding was a lack of correlation of time of presentation, levels of inhalational agents, or hemodynamic variables. From this series, the data suggest that time of presentation does not modulate stimulus acquisition during anesthesia.

<u>Discussion</u>. The results suggest a persistence of the acquisition of auditory information throughout adequate surgical anesthesia. Patients' <u>verbal retrieval</u> abilities are therefore unreliable indicators of <u>sensory responses</u> to intraoperative auditory events. These results confirm neurophysiological findings of preservation of evoked auditory potentials throughout surgical anesthesia. Statements during general anesthesia which direct patient behavior may therefore be effective despite postoperative verbal amnesia.

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Title: TOURNIQUET PAIN: CHANGES IN SSEP, BLOOD LACTATE AND VENOUS BLOOD GASES

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Introduction. We investigated the effect of tourniquet application on: 1) somatosensory evoked potentials (SSEP), 2) blood lactate (L) and 3) venous blood gases (VBG). The lactate levels were determined to see if the postdeflation pain is due to washout of accumulated metabolic products (1).

Methods. The study was approved by the Human Subjects Committee of Northwestern University and the Research Committee of Northwestern Memorial Hospital. Eight male, unmedicated, healthy volunteers, aged 26-39 were studied. Baseline determinations, before application of the tourniquet (T), included the following: 1) pain visual analog scale (VAS) score, 2) blood withdrawal for L and VBG (pH, PCO2, PO2, O2Hb saturation) from an IV cannula inserted into an antecubital vein, and 3) ulnar nerve SSEP. The VAS was a 100 mm line, the 0 end states "I have no pain at all," the 100 mm end states "I feel the worst pain imaginable." Lactate levels were determined by the Du Pont Automatic Clinical Analyzer (ACA); the blood gases were determined by IL Blood Gas Analyzer 813 and IL Cooximeter 282. A multichannel signal averager (Nicolet Pathfinder I) was used to determine and record SSEPs, the technique has been described previously(2). A pair of surface electrodes were placed over the ulnar nerve at the wrist; recording electrodes were placed 1) over the ulnar nerve at the ulnar groove at the elbow, 2) at the ipsilateral Erb's point, and 3) at the contralateral scalp over the neuronal generator areas (C3' or C4'). Peak to peak amplitudes and latencies of the composite responses from all 3 recording sites were monitored and recorded. After exsanguination of the upper extremity with an Esmarch bandage, a 7 cm T was applied at the mid upper arm with soft roll under it. Inflation pressure was 100 mm Hg over the systolic blood pressure, the T was applied until the pain was unbearable. VAS scores were taken every 5 minutes and SSEP recordings were done every 5-10 minutes during T inflation. After T deflation, blood for L and VBG were withdrawn: 1) immediately, b) 2, 5, 10, 15 minutes for the first 4 volunteers, and c) additionally at 30, 45 and 60 minutes for the last 4 volunteers. The SSEP were recorded at 5 minutes then every 10-15 minutes for 45-60 minutes after deflation. Repeat measures ANOVA and Bonferroni paired t tests compared the changes in L and VBG. A 50% or more decrease in the amplitude and 10% or more prolongation of the latency were considered significant (3).

Results. There was a gradual increase in the VAS; maximum scores were 90-100. Mean (+ SD) T time was 36.2 ± 11 min (range: 25-55 min). Pain was relieved with deflation, this recurred (reperfusion pain, RP) in 5 of 8 volunteers. RP occurred at 30-120 seconds after deflation and lasted 75-120 seconds. Tourniquet time was 41 ± 11.4 minutes in the volunteers who experienced RP compared to 28.3 ± 5.8 in those that did not. The L levels still significantly elevated at 5 and 10 minutes after deflation (Table 1) when RP was already gone.

There was a consistent increase in venous $\mathbf{0}_2$ and $\mathbf{0}_2$ Hb saturation for 5-10 minutes after T deflation. The Erb's and cortical SSEP amplitudes were abolished with T inflation while the ulnar nerve amplitude at the elbow, though significantly depressed, was not (Table 2). The SSEP amplitudes increased and the latencies improved toward baseline values at the conclusion of the study.

Discussion. Unlike Yamada's study (4) which followed the Erb's and cortical amplitude, we also recorded the amplitude of the ulnar nerve at the elbow. The depression of the SSEP at the elbow is solely due to ischemia while the abolition of the Erb's and cortical amplitudes is due to nerve compression and ischemia. RP is probably not related to washout of anaerobic metabolites since L was still elevated for several minutes after RP was gone. The elevated PO2 and L levels when blood flow has been restored for several minutes reflect continued anaerobic muscle metabolism; this maybe due to persistent capillary narrowing or closure that started during the period of ischemia (5).

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Table 1. Lactate (L) and YBG Changes

	В	THUTEO.		- 5	10	15	30	45	-60
L	9+4	28+9*	20+5*	18+2*	18+3*	15+3	_0 <u>+1</u>	9 <u>+1</u>	721
pК	7.37 <u>+</u> .03	7.30 <u>+</u> .04*	7.38±.02	7.4 <u>+</u> .02	7.4 <u>+</u> .02	7.4 <u>+</u> .02*	7_4 <u>+</u> .02	7.4+.02	7.41 <u>+</u> .01
PCO2	50 <u>+</u> 4	63 <u>+</u> 9*	47 <u>+</u> 4	43 <u>+</u> 3*	44+2*	44+4*	48 <u>+</u> 3	45 <u>+</u> 3	45 <u>+</u> 3
P02	33 <u>+</u> 6	41 <u>+</u> 15	63 <u>+</u> 15*	63 <u>+</u> 14*	54 <u>+</u> 12*	48 <u>+</u> 13	44 <u>+</u> 17	50 <u>+</u> 18	44+16
O2Hb Satn.	62 <u>+</u> 11	63 <u>+</u> 22	90 <u>+</u> 6*	91 <u>+</u> 4*	82 <u>+</u> 13	74 <u>+</u> 20	66 <u>+</u> 18	73 <u>+</u> 17	69 <u>+</u> 6

 Table 2. SSEP Amplitude (A) and Latency (L) Changes

 TOURNIQUET + TOURNIQUET +

 SSEP
 ELBOW
 ERB'S
 CORTEX
 ELBOW
 ERB'S
 CORTEX

 A: % D
 84 + 16 100 + 0 100 + 0 3 + 6 4 + 10 2 + 6
 4 + 10 2 + 6

 L: % P
 92 + 21
 -*
 -*
 4 + 3 3 + 4 1 + 2

D = Depression P = Prolongation * Cannot be determined, A was abolished.

itle: uthors: A TECHNIQUE FOR CONTINUOUS LUMBAR SYMPFTHETIC BLOCKADE FOR SEVERE REFLEX SYMPATHETIC DYSTROPHY

IN CHILDREN AND ADOLESCENTS

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Introduction. Although children with reflex mpathetic dystrophy may improve with inservative therapy, 1 there is a subgroup with evere involvement who may benefit from mpathetic blockade. For children and lolescents, either sedation or general anesthesia often required for adequate cooperation. sultant sleepiness or nausea following sedation or multiple intermittent blocks impedes physical nerapy and behavioral treatments. Multiple ocks under fluoroscopic guidance produce gnificant radiation exposure. For these asons, we have used continuous sympathetic ockade via a catheter. There is brief mention textbooks of continuous blockade in adults, t there are no detailed reports regarding chnique or outcome.

Methods. Five patients, ages 11 to 19, were und to be refractory to aggressive conservative erapy and were scheduled to have sympathetic ockade. Two had previously received termittent sympathetic blockade. Parental and tient informed consent was obtained. travenous sedation was administered. Following filtration with local anesthetic, needles were vanced in standard fashion^{2,3} 5 to 6 cm lateral L2 and L3 spinous processes. Needle tip sition was confirmed by loss of resistance.

ntrast injection, and flouroscopy.

Instead of the over-the-needle catheters used eviously (which are easily placed but may ide, kink, or break), 20 gauge epidural theters (marked to 30 cm) were passed through 17 uge 7 inch Tuohy-Weiss needles. Each catheters advanced 2-3 cm past the end of the needle, e needle was withdrawn, depth was determined, d the catheters were secured. Following test sing and confirmation of blockade by skin mperatures and clinical effect, repeat dosing upivacaine 0.25% 15-20 cc) was performed three four times daily for five to seven days.

Results. Catheters were placed on 7 casions in 5 patients, as shown in Table 1; The produced sympathetic blockade onsistent temperature rises of greater than 4 grees C, increased perfusion, and diminished alling) in every case. No complications curred. Catheter migration (defined arationally when injection produced an significant temperature rise) occurred on 3 casions. Initial placement of catheters at both and L3 permitted continued treatment via the ner catheter in these cases, obviating the need an additional needle procedure. Three of the re patients achieved long-term relief of pain d good function. (One patient had a brief lapse which responded well to a second course of ntinuous blockade. One patient has persistent in despite improved functioning after two

courses of continuous blockade.

Discussion. Continuous lumbar sympathetic blockade can be an effective treatment for refractory reflex sympathetic dystrophy in children and adolescents. In our view, use of paravertebral selective sympathetic blockade is preferable to continuous lumbar epidural blockade because of: (1) longer duration of sympathetic blockade following intermittent injection, (2) preservation of strength, sensation and normal micturition, and (3) confirmation of the clinical diagnosis with selective blockade.

Patient acceptance of the continuous technique was better than that observed previously for 6 adolescents undergoing intermittent lumbar sympathetic blocks. If sympathetic blockade is chosen for children or adolescents, we recommend continuous blockade from the start.

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lable 1.	Continu	ous Lumbar	Sympathetic E	llockade	
Patient	1	2	3	4	5
Age (years)	15	19	14	11	16
Site(s)*	R foot	R foot	R & L LE	L foot	L ankle å foot
Prior Duration of Symptoms (months)	5	32	4	12	7
Duration of follow-up (months)	10	11	6	2	0.5
Prior/current pain severity⇔	3/0	3/1	3/2	2/0	3/3
Prior/current functional level***	0/3	0/2	0/1	1/3	0/0
Time to achieve minimal or no pain/ Time to achieve good or excellent functional level (weeks)	2/3	2/4	-/-	1/2	-/-

^{*} R and L denote right and left, respectively, LE denotes lower extremity;
** pain is rated subjectively as: 0 - none, 1 - mild, 2 - moderate, 3 -
severe; *** functional level is defined as 0.- unable to tolerate weightbearing or touch, 1 - severe limp, 2 - normal gait but unable to run
(good), 3 - able to tolerate vigorous exercise (excellent).

EPIDURAL ANESTHESIA AND WATER IMMERSION FOR EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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Introduction: Extracorporeal shock wave lithotripsy (ESWL) is a widely used non-invasive alternative to surgical treatment of kidney and ureter stone disease. ESWL presents a unique anesthetic challenge both because it involves water immersion in the semi-supine position and stimulation from the treatment that can be ablated by lower levels of anesthesia than would be required for many other surgical procedures. ESWL allows for and demands greater flexibility in anesthetic management. This has lead to various anesthetic techniques (general anesthesia, epidural anesthesia(1), intercostal narcotic/sedative) being blocks, and nerve successfully employed in selected groups of patients. General anesthesia is felt to offer the advantages of decreased respiratory motion (if "high frequency" ventilation is employed) which may allow the use of a lower number of shocks, as well as more rapid patient preparation time. No single anesthesia technique has proven superior. General anesthesia and water immersion may significantly reduce lung volumes and increase airway pressure. The effects of epidural anesthesia on pulmonary function has been documented, but the combined effects of epidural anesthesia and water immersion on lung volumes and flows have not been studied. We studied the effects of epidural anesthesia and water immersion on pulmonary volumes and flows.

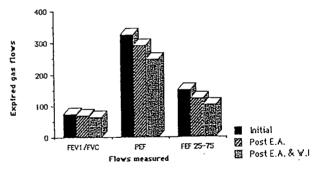
After approval of the Human Studies Committee and with patient permission, eight subjects were studies. Subjects ranged in age from 39 to 65 years. All subjects were males. Four patients were smokers and four were non-smokers. included illnesses medical Intercurrent bronchospastic disease (one subject), ASCVD (two), hypertension (one), and NIDDM (one). The subjects weight ranged from 62 to 120 kilograms. No perioperative cardiac or respiratory complications were noted. All patients received epidural anesthesia with a sensory level of at least T4 (to stimuli). Routine monitoring included continuous ECG, an automatic blood pressure device, and pulse oximetry. Local anesthetics and techniques were used at the discretion of the anesthesiologists. Lung volumes and flows (FVC, the FEV1, FEV 1/FVC, PEFR, and FEF 25-75) were measured in a semi-upright position (to simulate patient position in the ESWL gantry) before initiation of epidural anesthesia, after T4 sensory level was obtained and after water immersion with epidural anesthesia at T4 sensory level. The best values for each parameter from three successive spirometric attempts were chosen for analysis. The spirometer used was a Respiradyne Pulmonary Function Monitor, model # 5-7905.

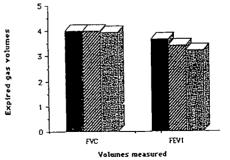
Results: FVC decreased in six of eight subjects, FEV 1 decreased in seven of eight, FEV 1/FVC decreased in five of eight, PEFR decreased in seven of eight, and FEF 25-75 decreased in five of eight subjects with initiation of epidural anesthesia and/or water immersion. (Refer to Figure 1) However, the changes between pre-anesthetic, T4 epidural anesthesia and water immersion did not reach statistical significances. There were no significant changes noted in oxygen saturation, respiratory rate, cardiac rate or rhythm, blood pressure, nor were subjective feelings of dyspnea reported.

Discussion: General anesthesia entails significant reduction in lung volumes and increase in airway pressure. These factors may lead to increased perioperative morbidity(2,3) and nortality(4). Water immersion, a semi-supine position and epidural anesthesia were expected to produce significant decreases in measured pulmonary volumes and possibly in gas flows(5,6). Our preliminary results indicate a lack of significant changes in lung volumes and gas flows with epidural anesthesia both before and after water immersion. Thus, we were able to provide analgesia without altering selected lung parameter and this may represent an advantage of epidural anesthesia over general anesthesia during ESWL.

FIGURE 1

FLOW AND VOLUME CHANGES WITH EPIDURAL AMESTHESIA (E.A) AND WATER IMMERSION (W.I.)





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ADENOSINE AGONIST DECREASES HALOTHINE MAC AND NORADRENERGIC NEUROTRANSMISSION IN RATS

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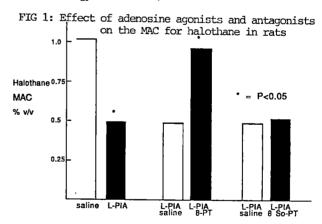
Introduction. Central monoaminergic neurotransmision exerts an important role in modulating the epth of the anesthetic response. Earlier we emonstrated that aminophylline (the A_1 adenosine itagonist) enhances noradrenergic neurotransmission id decreases anesthetic responsiveness1. irrent study was designed to test the converse, e. to determine if L-phenylisopropyladenosine (L-A), a potent A_1 adenosine receptor agonist hances the halothane-anesthetized state. we effect of L-PIA on neurotransmission in both the radrenergic and dopaminergic pathways was assessed iring halothane anesthesia. To determine if action ι central or peripheral adenosine receptors was sponsible for any observed change, separate MAC periments were performed with co-administration of e adenosine antagonist 8-phenyltheophylline (8-PT) 8-sulphophenyltheophylline (8-So-PT; a polar rivative of 8-PT which does not cross the blood-

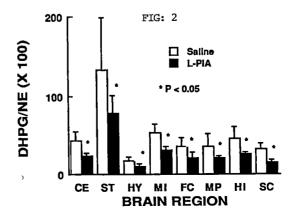
ain barrier). . Halothane MAC was determined in male <u>Methods</u>. rague-Dawley rats (250-300g) as previously scribe2. One half of the responding and nonresnding cohorts (n=8 each) received L-phenylisoproladenosine (L-PIA) 1 mg/kg i.p.; the other half ceived an equal volume of saline i.p.. MAC was termined $\times 2$ at 30-min intervals. The involvement central and not peripheral adenosine receptors s tested by administering 8-phenyltheophylline (8-), 2.5 mg/kg and 8-sulphophenyltheophylline (8-So-), 30 mg/kg. These antagonists were injected 10 n prior to L-PIA in additional MAC experiments. determine the effect of L-PIA on neurotransmison, rats were anesthetized with 1.2% halothane and ter 1 h, were injected i.p. with either L-PIA, 1 /kg (n=7), or an equivalent volume of saline =7). Neurotransmission in the respective pathways 1 be measured by determining steady-state turnover r the monoamines in functionally and anatomically screte areas of rat brain. The rats were decapitai after 60 min and the frontal cortex (FC), pocampus (HI), hypothalamus (HY), midbrain (MI), lulla-pons (MP), cerebellum (CE), Striatum (ST), is spinal cord (SC) were dissected. Norepinephrine
and dopamine (DA) turnover in these brain
sions was measured as previously described. MAC ues were compared for statistical significance by llysis of variance (ANOVA) for repeated measures. itistical differences in the ratio of the metaboe dihydroxyphenylethylene glycol (DHPG), dihydrphenylacetic acid (DOPAC) to the parent monoamine , DA respectively) concentration between the L--treated and control animals were compared by the aired t test for each brain region and a P -value <0.05 was considered the level for significance. esults. L-PIA treatment led to a 49% reduction MAC (Fig 1). This change was abolished by coch freely permeates the blood-brain barrier; treatment with 8-So-PT, the non-permeant A₁ nosine antagonist, had no effect (Fig 1). adrenergic neurotransmission (reflected by the io of DHPG/NE) was significantly diminished lowing L-PIA treatment in all brain regions (Fig Dopaminergic turnover was unaffected.

Discussion. Central adenosine receptors appear to mediate the L-PIA reduction of halothane MAC by decreasing noradrenergic neurotransmission. These data support the conclusion that noradrenergic neurotransmission is a critical modulator of the anesthetic response. The results of this study provide implications for the use of adenosine, as well as drugs that alter its activity, in anesthetic settings. Thus the use of adenosine and ATP for induced hypotension may profoundly reduce MAC and increase the anesthetic response. Although dipyridamole inhibits adenosine metabolism, it would probably not effect the anesthetic state due to its inability to penetrate the blood-brain barrier. Children with adenosine deaminase deficiency and patients treated with the adenosine deaminase inhibitor, deoxycoformycin for acute lymphoblastic leukemia would be expected to exhibit a decrease in halothane anesthetic requirements.

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Title: SUBARACHNOID & EPIDURAL CALCITONIN FOR THE MANAGEMENT OF CANCER PAIN

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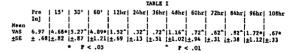
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Introduction. Salmon Calcitonin (sCT) has been found to produce analgesia when injected IM, IV or SC. In addition, subarachnoid (SA) and Epidural (Epi.) injections of sCT have provided analgesia in patients with oncological pain and post operative pain. (1,2,3) The present study was undertaken to evaluate the effectiveness of calcitonin for the management of patients with severe cancer pain and investigate the effectiveness of the Epidural route in patients who developed analgesia after Subarachnoid administration.

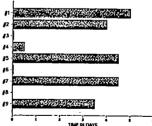
Methods. After gaining approval from the Institutional Review Board and obtaining informed consent, nine patients were enrolled in the study. All patients had metastatic cancer and reported severe pain with failure to respond to traditional therapies. The patients pain level prior to drug administration was evaluated by having the patient mark a 10 centimeter Visual Analog Scale (VAS). PT and PTT were performed prior to injection and serun calcium levels were measured pre and post injection. The SA space was entered at the L_-L_ interspace and 100 units of sCT diluted in 5 ml. of normal saline was injected slowly over one minute. The patients were asked to mark the VAS after the injection at 15 minutes, 30 minutes, 1 hour, 12 hours and continuing every 12 hours until the pain returned to the original level. The patients who reported analgesia after the SA sCT were given an Epi. injection of 200 units of sCT diluted in 10ml of normal saline when their pain returned to pre SA injection level. The patients were followed and their analgesia evaluated in the same manner until the pain reached the original level. The degree of pain relief was compared to pre treatment levels and differences were subjected to statistical analysis using the paired t-test.

Results. Eight out of the nine patients (89%) reported significant analgesia after SA sCT. Some patients experienced pain relief for a short duration, while in others, pain relief lasted up to five days (see graph #1). When comparing post injection VAS to pre injection VAS, data showed a significant decrease in pain levels during the first 30 minutes and from 12 hours through 108 hours post SA sCT (see table #1). Four patients who had analgesia after the SA sCT were given Epi sCT. Of these patients, 2 (50%) reported pain relief, one for four days, one for one day, and 2 patients had no relief. The other four patients who had relief after the SA sCT refused the Epi. injection due to the side effects of nausea and vomiting. Seven of the nine patients who received SA sCT reported significant nausea and vomiting. One patient had a focal seizure 12 hours after the SA sCT injection with post ictal depression but recovered fully. Serum calcium levels post SA injection were significantly lower when compared to pre injection levels. Although the changes were statistically significant, they were too small to be of clinical significance (mean pre-injection $9.61 \pm .28$; post injection 9.17 \pm .25).

Discussion. Subarachnoid and Epidural Salmon Calcitonin produced significant analgesia in our study patients as had been previously demonstrated another studies (1,2,3). The exact mechanism of action is unknown, but it is considered that sCT may interfere with prostaglandin synthesis by inhibiting the enzyme cyclooxygenase and this results in less prostaglandin mediated hyperactivity in spinal neurons. In our study there was a 78% incidence of nausea and vomiting while in the studies of Fraioli et al. and Miralles et al. there was a 38% and 6% incidence respectively (2,3). It is unclear why our patients had such a high incidence of this side effect. The number of patients who received Epi. sCT was very small and it is not possible to make any significant conclusions but it appears that Epi sCT may not be as effective as SA sCT. SA sCT produces analgesia but in this study it was accompanied by significant nausea and vomiting. The patient who developed a seizure had cranial metastases and it was not possible to determine if this event was due to the SA sCT or attributable to other causes. Indeed, further research in a larger population of patients is needed regarding prevention of nausea and vomiting, evaluation of side effects and possible long term analgesia by Subarachnoid Calcitonin or the attainment of comparable pain relief and duration by the Epidural



GRAPH I SUBARACHNOID CALCITONIN DURATION OF PAIN RELIEF



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Title: GUANFACINE REDUCTION IN HALOTHANE ANESTHETIC DOSE REQUIREMENT IN DOGS

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<u>Introduction:</u> Guanfacine (TENEX^R) has been recently introduced as a centrally acting antihypertensive agent similar to clonidine but with far less sedation. Both agents are potent central alpha-2 adrenergic agonists. Clonidine has been shown to decrease halothane (50%)¹ and narcotic (40%)² anesthetic requirements while stabilizing hemodynamics. This study was undertaken to examine the hemodynamic effects and anesthetic requirement of acute guanfacine during halothane anesthesia in the dog.

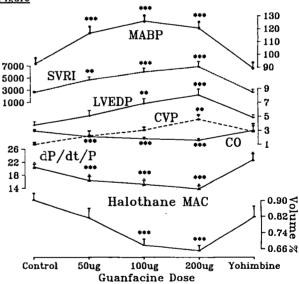
Eight mongrel dogs were induced by mask Methods: and intubated under deep halothane anesthesia. They were instrumented with a Millar micro-transducer-tipped catheter in the left ventricle to measure left ventricular end-diastolic pressure (LVEDP) and to derive dP/dt/P. A Swan-Ganz catheter was placed into the pulmonary artery for measurement of cardiac output (CO), central venous pressure (CVP) and core temperature. The femoral artery and vein were cannulated to measure mean systemic arterial blood pressure (MABP), and to allow blood sampling for catecholamine assays, and administration of fluids and drugs respectively. Halothane concentrations, pCO2 and determined by Perkin-Elmer mass pCO2 and pO2 were spectrometer. Heart rate was determined from ECG (lead II). All parameters (except CO) were continuously recorded on a multi-channel oscillograph. Standard methods³ (tail clamping) were used to determine minimum alveolar anesthetic concentration (MAC). After at least 1 hour of stabilization, control MAC was determined. Three doses iv. of guanfacine (50, 100, 200 ug/kg) were given at 25 ug/kg/min. Thirty minutes, following each dose MAC determinations minutes following each dose MAC determinations were begun. After the final guanfacine dose, 3 dogs were given yohimbine, a selective alpha-2 antagonist, and MAC was redetermined. Hemodynamic measurements were made and blood samples were taken prior to tail clamping. Hemodynamic values reported are the mean of the two values taken at the halothane levels which bracketed the MAC determination. All values reported are mean ± standard error of the mean (SE). Analysis of variance for repeated measure followed by Bonferroni modified t-test was used to determine statistical significance. Statistical significance was assumed at p<0.05.

Results: Control halothane MAC was 0.89 ± .04% Guanfacine end-tidal concentration. reduced halothane anesthetic requirement by 10%, 25% and 28% for the 50, 100 and 200 ug/kg doses respectively (Figure). At equipotent anesthetic levels, guanfacine administration resulted in an increase in MABP, systemic vascular resistance index (SVRI), CVP and LVEDP with a concomitant decrease in CO and dP/dt/P (Figure). Also, catecholamine levels, both epinephrine (EPI) and norepinephrine (NE), decreased significantly (p<0.01) to below detectable levels after an iv. guanfacine dose of 100 ug/kg.

Yohimbine 300 ug/kg completely reversed the guanfacine-induced halothane anesthesia potentiation and returned all hemodynamic parameters to control

Discussion: The centrally acting alpha-2 adrenergic agonist clonidine demonstrated to has been both inhalation and narcotic notentiate anesthesia.1,2 Guanfacine, a new drug in this class, is reported to cause less sedation and to have minimal alpha-1 adrenergic activity. Our findings show that guanfacine gave a smaller reduction of anesthetic MAC compared to clonidine. These results indicate that guanfacine, under the conditions described, increased rather than decreased MABP and SVRI. Both anesthetic sparing and hemodynamic effects were reversed by the selective alpha-2 adrenergic antagonist yohimbine.





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Title: EFFECT OF THEOPHYLLINE ON THE CEREBRAL BLOOD FLOW RESPONSE TO HYPOXEMIA

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Introduction: The delivery of an adequate supply of oxygen is essential for normal brain function. To this end, cerebral blood flow (CBF) and cerebral oxygen delivery (CO2D) remain nearly constant over a wide range of perfusion pressures and arterial oxygen contents. Failure to provide adequate CO2D can produce clinically detectable brain dysfunction (1). CBF increases in response to hypoxemia thereby preserving CO2D. The mechanisms producing this increase in CBF remain unclear, but adenosine, a potent cerebral vasodilator, has been proposed as a potential mediator. Theophylline is a potent adenosine antagonist and blocks adenosine mediated cerebral vasodilation in animal models (2). If adenosine plays a major role in the human CBF response to hypoxemia, theophylline should limit the ability of the cerebral vasculature to respond, resulting in a diminution of oxygen delivery to the brain.

While theophylline is a systemic vasodilator, it is a cerebrovascular vasoconstrictor. In customary therapeutic doses, theophylline reduces resting CBF in patients with COPD (3). If theophylline not only decreases resting CBF, but also interferes with the cerebrovasodilatory response to hypoxemia, an essential compensatory mechanism would be lost, representing a clinically significant side effect from a commonly employed therapeutic agent.

We therefore studied, in five healthy adult

peutic agent.

We therefore studied, in five healthy adult volunteers, the effects of moderate hypoxemia and therapeutic doses of aminophylline on CBF and CO2D.

Methods: Written informed consent was obtained from each volunteer to participate in a protocol approved by our institutional research practice committee. All volunteers were males in good

from each volunteer to participate in a protocol approved by our institutional research practice committee. All volunteers were males in good health.

We continuously monitored arterial O2 saturation (\$a02) with a pulse oximeter and end-tidal CO2 (ETCO2) with a capnometer. Heart rate and rhythm were monitored continuously with an oscilloscope and rate-meter and blood pressure was determined by auscultation at three-minute intervals. An intravenous catheter was inserted into a forearm vein and a tight fitting non-rebreathing face mask was applied through which the subject breathed during the entire study.

The subject then lay supine with his head fitted into a helmet containing 16 cadmiumtelluride gamma detectors (8 per hemisphere) placed over homologous brain regions corresponding with the international 10-20 electroencephalographic electrode system. CBF, as CBF15, was measured using the xenon-133 washout technique.

All subjects underwent four consecutive cerebral blood flow measurements during conditons of normoxemia and hypoxemia, before and after theophylline administration. Theophylline was administered as aminophylline, its ethylene diamine salt. Each CBF measurement required eleven minutes and was made in a quiet, darkened laboratory. CBF was first measured (N) during normoxemia with the subject breathing room air after a 20-minute acclamation period to accomodate to the instrumentation and laboratory surroundings. The second measurement (H) was made during inhalation of an oxygen/nitrogen mixture adjusted to maintain an SaOZ of 80%. The subjects were permitted 15 minutes for equilibration while breathing the hypoxic mixture before measurement of CBF. During the third measurement of CBF (A+N), subjects breathed room air following an infusion of 6 mg/kg aminophylline. We made the fourth CBF measurement (A+H) after 15 minutes of maintaining the subject's SaOZ at 80% and within 40 minutes of aminophylline loading. Hypoxemia can increase minute ventilation leading to hypocapnea which, in turn, decreases CBF

the inspiratory gases to match the ETCO2 present during the preceding normoxemic phase.

CO2D was calculated and expressed as a percent of the normoxemic value (CO2D%):

CO2D% = (SaO2 x CBF) / (SaO2 x CBF)normoxemia

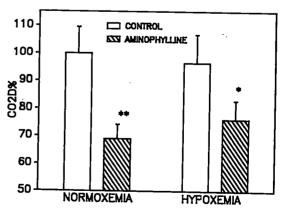
A repeated multivariate analysis of variance was performed to test for an overall time effect for CBF, CO2D%, SaO2, ETCO2, HR, and MAP. When a significant time effect was detected paired t-tests were conducted to assess specific differences of interest.

Results: The figure displays mean (±SE) CO2DZ for each study condition. CBF (mean ± SE) increased significantly from N to H (43.8 ± 3.6 to 51.3 ± 5.1 ml/100g/min; p<.05). This increase in CBF served to preserve CO2DZ during hypoxemia at normoxemia levels (p>.3). Following aminophylline there was a significant reduction in normoxemic CBF (30.1 ± 2.0; p<.003) and CO2DZ (p<.01). The induction of hypoxemia augmented CBF (A+H CBF = 40.7 ± 3.4; p<.02). Despite this increase, the A+H CO2DZ fell significantly below the CO2DZ during H (p<.05).

Discussion: In hypoxemic as in normoxemic man, aminophylline decreases CBF and, therefore, reduces CO2D. In usual clinical doses, aminophylline, a potent adenosine antagonist, does not prevent the hypoxia-related increase in CBF but the absolute levels of CBF and CO2D are reduced. This represents a potentially significant interference with an important physiologic compensatory mechanism by a commonly used therapeutic agent.

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CEREBRAL OXYGEN DELIVERY Z versus STUDY PERIOD



+=p(.05; ++=p(.01 compared to control value

Title: MIVACURIUM CHLORIDE (BW B1090U) INFUSION REQUIREMENTS IN CHILDREN DURING HALOTHANE OR NARCOTIC ANESTHESIA

Authors: BW Brandom, M.D., JB Sarner, M.D., ML Dong, M.D., M Horn, M.D., SK Woelfel, M.D., DR Cook, M.D.,

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Introduction. Mivacurium (BW B1090U), a shortacting nondepolarizing neuromuscular blocking agent, is efficacious as an infusion (1,2). We determined the infusion rates of mivacurium required to maintain a near steady state of neuromuscular blockade in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia.

Methods. Thirty-one children (ASA status I-II) between 2 and 12 years old, having low risk elective surgical procedures were studied. The study was approved by the Human Rights Committee of the Children's Hospital of Pittsburgh; informed consent was obtained from a parent. No patient received aminoglycoside antibiotics or antihistamines within 48 hours of the study. The patients were divided into two groups; those receiving nitrous oxidehalothane (HAL; N=10) and those receiving nitrous oxide-narcotic anesthesia (BAL; N=21). The children in the HAL group were not premedicated. Anesthesia was induced with nitrous oxide (70%), oxygen (30%) and halothane (up to 4% inspired). An intravenous catheter was placed and atropine (10 µg/kg) was given. End-tidal halothane concentration was adjusted to 0.3 + 0.05%; fentanyl (1-3 µg/kg) was given as needed. The children in the BAL group were premedicated with diazepam (0.1-0.2 mg/kg) by mouth. Nitrous oxide was administered by mask, an intravenous catheter was placed, and thiopental (4-10 mg/kg), diazepam (0 to 0.2 mg/kg), and fentanyl (2-6 µg/kg) were given. Anesthesia was maintained with nitrous oxide (70%) and fentanyl.

The ulnar nerve was stimulated supramaximally with repetitive trains-of-four stimuli (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan Bennett/Datex monitor. The degree of neuromuscular block was described as percent of control in that the height of the first train-of-four response (T1) was compared to the control EMG height. Blood was obtained for measurement of pseudocholinesterase activity (PA) and dibucaine number.

An IV bolus dose of mivacurium was administered; neuromuscular block was observed. A second bolus dose was then administered to establish 100% block. After recovery to 5% of baseline, an infusion of mivacurium (0.5 mg/ml in 5% dextrose) was begun at 10 µg/kg/min and titrated to maintain 89% to 99% neuromuscular blockade. The infusion rate required to maintain blockade in the desired range was calculated for each patient. Spontaneous and neostigmine induced recoveries were recorded. T25-T75 was the time in which the first twitch in the train-of-four recovered from 25% to 75% of baseline. $T4/T1 \ge 0.75$ was the time from the termination of infusion to the time train-of-four ratio was greater than 75% during spontaneous recovery. Recovery was referenced to final baseline.

Standard errors (SEM) are shown for all mean values. Differences in the mean values were compared by t-test. Regression analysis was used to identify factors varying with infusion rate. Statistical differences were considered significant at P < 0.05.

Results. There were no significant differences between the groups with respect to age or body surface area. Normal PA was 2.5-7.1 U/L and normal percent inhibition by dibucaine was 70-95%. No patients had low PA. One patient had a subnormal dibucaine number (60% inhibition with a PA of 5.2 U/L) and an infusion requirement of 15.3 µg/kg/min. Two patients in the HAL group had abnormally high PA (7.5 and 10.6 U/L) and infusion requirements of 21.8 and 37.6 µg/kg/min respectively. When these three patients were removed from the analysis, there was a statistically significant difference between infusion requirements with anesthetic background using a one tailed t-test only (Table 1). There was a statistically significant positive relationship between infusion rate and PA (R=0.76) considering all 31 patients.

The spontaneous recovery parameters were also similar in the two groups (Table 1). Spontaneous recovery of the initial stwitch to 95% of baseline occurred within 9 to 14 minutes of the end of the infusion. Neostigmine (0.05-0.06 mg/kg) was given to eight patients 2 to 7 minutes after termination of the mivacurium infusion, when T1 was at least 13% (average recovery 25%). T4/T1 increased to 75% within 1.2 to 2.8 minutes after administration of neostignine.

Discussion. In this study the mivacurium infusion requirement was slightly less during nitrous oxide-halothane anesthesia than during nitrous oxide-narcotic anesthesia. Infusion requirement was related to PA under both anesthetic conditions. The average infusion rate required to maintain 89%-99% block in children under nitrous oxide-narcotic anesthesia is greater than the rate previously reported by us in adults during ritrous oxide-narcotic anesthesia (3).

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Table 1. Neuromuscular Effects of Mivacurium

			± SEM ange)	
	Infusion Rate	Length of Infusion	T25-75	T4/T1 > 0.75
	μg/kg/min	min	min	min
HAL	*12 <u>+</u> 2 (5-19) N = 8	$^{141} + ^{6}$ $^{(10-80)}$ $^{N} = ^{10}$	$3.4 \pm 0.4 (1.8-4.5) N = 6$	$ 9.9 \pm 0.4 \\ (8.8-10.5) \\ N = 4 $
BAL	*16 + 1 (9- $\overline{3}1$) N = 20	50 ± 7 (17-137) N = 21	4.0 ± 0.3 (2.6-6.2) N = 12	10.5 ± 0.6 (7.5-15.2) N = 12

*Statistically significant differences; one tailed t-test

Title: EVALUATION OF EMLA (EUTECTIC MIXTURE OF LOCAL ANESTHETICS) FOR TOPICAL ANALGESIA IN

CHILDREN

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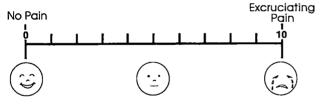
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A new formulation based on the eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA) has become available for clinical testing in the United States. The compound has been previously tested in Europe on adults and premedicated children. The purpose of this study is to evaluate the efficacy of skin analgesia produced by EMLA for preoperative venous cannulation in a group of otherwise healthy, unpremedicated children.

Methods: Institutional approval and parental consent were obtained for this open-label, non-randomized study. Twenty-two ASA PS I unpremedicated children ages 7-12 vrs agreed to participate in the study. EMLA 5% cream (2.5 gm) was applied to the skin overlying a preselected vein on the dorsum of one hand and covered with an occlusive dressing (TEGADERM). After at least 60 minutes, the cream was removed and the skin inspected for changes or reactions. The quality of analgesia produced by the EMLA cream was tested by making a "nick" on the dorsum of the hand with the bevel of a 19 gauge needle. This was followed by the insertion of a 20 gauge intravenous (iv) catheter (Cathlon IV) into the underlying vein. The pain response of the child to these events was subjectively assessed by the anesthesiologist performing the cannulation and objectively quantitated by both an independent observer and the child, using a 0-10 visual analogue pain scale (figure).

LINEAR ANALOGUE PAIN SCALE



In addition, the degree of cooperation obtained from each child was rated by the observer using a 5 point scale (1-fully cooperative; 5-combative, required restraining). The skin was again examined for any reaction either when the intravenous cannula was removed, or 4-6 hours following EMLA application if the iv was still in place. comparison, the pain ratings for the EMLA children were contrasted with those observed in a matched control group of 20 children in whom preoperative phlebotomy was performed with a 23 GA needle without any form of skin analgesia. Differences in the response of the children to the EMLA venipuncture and standard phlebotomy were examined. The data was analyzed using Spearman's rank agreement between correlation to compare corresponding pain scores awarded by each patient and the observer. The Wilcoxon rank sum test was used to compare differences between the observer's, and the patient's assessment of pain intensity during cannulation and/or phlebotomy.

Results: The two groups did not differ in regards to age (mean 9.7 yrs) and there was no correlation between age and pain scores. It was the opinion of the anesthesiologist performing the venous cannulations following EMLA

application that all, except one child, in this group had topical anesthesia. When the children rated their own pain. the two groups had identical median analogue pain scores of 3 (range 0-10). The observer rated the median pain score associated with EMLA venous cannulation at 0.5 (range 0-8), while that associated with phlebotomy was 1.0 (range 0-2). These differences are not statistically significant. children in both groups rated their pain and discomfort significantly higher than did the observer (p < .001). Cooperation ratings were identical for the two groups, with a median score of 1.0 (range 1-5). One nine year old child became agitated and diaphoretic immediately following application of the EMLA cream to her hand. This child was removed from the study and sent to the lab for routine phlebotomy where she once again became agitated, diaphoretic, and syncopal. Another EMLA child was removed from the study following application of the cream because the starting time of her surgery was moved up due to the cancellation of a previous case; thus, there was not sufficient time to permit the optimal 60 minute EMLA contact period. All the remaining EMLA patients had effective analgesia for their venous cannulation. However, one of these children was troubled by itching and another 7 sustained transient blanching of the skin over the EMLA contact area. Both problems resolved spontaneously and no treatment was required. There were no residual skin reactions at the time of iv removal in any of the children. The skin area where EMLA was applied continued to retain a greasy quality following removal of the cream with a tissue and alcohol. This condition made it necessary to pay special attention to the taping of the iv cannula in order to avoid accidental dislodgment.

<u>Discussion</u>: Many attempts have been made to obtain a suitable formulation of local anesthetics which will produce effective topical anesthesia, and therefore allow painless venous cannulation in awake unpremedicated children. When mixed in equal amounts, the solid pure bases of lidocaine and prilocaine constitute a eutectic mixture, which forms an oil at temperatures greater than 16°C. EMLA cream is an oil-in-water emulsion of these two bases.

It is our conclusion that EMLA cream produces effective topical anesthesia and alleviates the physical component of pain associated with venous cannulation and blood drawing in awake unpremedicated children. Objectively the pain and discomfort associated with 20 GA venous cannulation was no more intense than that associated with routine phlebotomy using a much smaller needle. Children rated the discomfort associated with these events significantly higher than did the observer. This may be due to the emotional component of pain perception, which is not altered by the use of skin analgesia.

Since 60 minutes contact time is required for EMLA to become fully effective, should the anesthesiologist fail to successfully cannulate a previously prepared vein, re-use of EMLA becomes impractical.

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THE EFFECTS OF PERITONSILLAR INFILTRATION UPON THE REDUCTION OF OPERATIVE BLOOD LOSS AND POSTOPERATIVE PAIN IN CHILDREN HAVING TONSILLECTOMIES

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Tonsillectomy is often associated with significant intraoperative bleeding and postoperative pain. Boliston and Upton (1) showed that local infiltration of lidocaine 0.5% and epinephrine 1:400,000 in the peritonsillar bed of adults undergoing tonsillectomy under general anesthesia resulted in greater ease in dissection and a significant reduction in operative blood loss. These authors did not evaluate the effect of peritonsillar infiltration upon postoperative pain relief. This study examines the effects of peritonsillar infiltration with three different solutions upon intraoperative blood loss and postoperative analgesia in children undergoing tonsillectomy.

Methods: The study was approved by the Institutional Research Committee, and informed consent was obtained from all parents. We studied forty-two unpremedicated ASA PS I children between four and twelve years of age who were undergoing tonsillectomy. Anesthesia was induced either with intravenous thiopental 6.0 mg/kg or by inhalation of nitrous oxide, oxygen, and halothane. Monitors included a precordial stethoscope, Dinemapp(R) oscillometer, electrocardiogram, and axillary temperature. In addition, end-tidal carbon dioxide was monitored and maintained at 37 + 2 torr throughout surgery. Anesthesia was maintained with nitrous oxide 70%, oxygen 30% and isoflurane 0.5 to 3%. Following intubation, a throat pack was placed in order to account for blood loss, which would otherwise have gone unrecognized because of gravitation into the stomach. Morphine sulphate 0.05 mg/kg and glycopyrrolate 0.01 mg/kg were administered intravenously prior to commencing surgery.

For the purpose of infiltration, patients were randomly assigned to one of four groups. Children in Groups I, II and II had their peritonsillar region infiltrated with the contents of a coded vial containing either bupivacaine 0.25% with epinephrine 1:200,000, normal saline with epinephrine 1:200,000, or normal saline. The maximum volume allowed to be injected in these children was 0.5 cc/kg. Group IV children had no infiltration (control). Blood loss was carefully measured by weighing the throat pack and sponges and by determining the volume of shed blood in the suction pottle with a graduated cylinder. Following awake extubation at the end of surgery, patients were observed for 50 minutes in the recovery room by a blinded observer and the severity of their pain was evaluated with an objective ten point pain scale. The objective scale equated the severity of pain with blood pressure elevation, crying, excitement, anxiety level and verbal reports of pain using a scale of 0-2 for each of the five categories. Morphine sulfate 0.05 mg/kg I.V. was administered in the recovery coom if the patient complained of pain or if a pain score of 5 or more points was obtained on two consecutive five ninute observations. On the ward, children were medicated with oral codeine elixir 0.5 mg/kg PO Q 2-3 hours orn. The total amount of morphine administered in the recovery room and codeine given on the ward during the first 12 postoperative hours were recorded, and the differences in the amounts required by each group were compared by chi square analysis. Differences in blood loss among the groups were compared using analysis of variance.

Results: The control group lost two to three times more blood than did the experimental groups (Table). There was no difference in the reduction of operative blood loss between the two drugs containing epinephrine (Group I and II). Group I and II were significantly better than saline alone, (Group III), in reducing intraoperative blood loss (p < .01). However, saline infiltration (Group III) did significantly reduce operative bleeding when compared to controls (><.001).

There was no significant difference in either pain scores or morphine and codeine requirements among any of There was no postoperative bleeding in any the groups.

OPERATIVE BLOOD LOSS AS % OF EBV*

	Group I	Group II	Group III	
	Bupivacaine with EPI 1:200,000	Saline with EPI 1:200,000	Saline	Control
_	N=10	N=10	N=10	N=12
Mean Loss ± SEM	1.50 ± .38	1.47 ± .48	2.40 ± .16	4.62 ± .43

*Estimated blood volume (EBV) = 70 cc/kg

Discussion: The operative blood loss associated with tonsillectomy can be reduced by using epinephrine infiltration. It can also be reduced by injecting volume (saline) into the peritonsillar region. We speculate that the solutions injected into the plane of dissection between the tonsillar capsule and pillar compressed vascular structures and thus reduced operating blood loss. Rupivacaine did not appear to provide significant postoperative analgesia. All groups required similar amounts of morphine and codeine for postoperative pain relief. We are unable to explain why tonsillectomies in adults can be performed with only local anesthetic infiltration and intravenous sedation, yet in children using a similar technique we obtained no objective postoperative pain relief.

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EPIDURAL LIDOCAINE FOR CESAREAN SECTION: MINIMUM EFFECTIVE EPINEPHRINE CONCENTRATION

Authors:

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Introduction. Lidocaine, 2%, is commonly used for epidural anesthesia for cesarean section, with 1:200,000 epinephrine added to decrease serum lidocaine concentrations and improve analgesic efficacy. The use of epinephrine in obstetric patients is controversial, however, because of its potential adverse effects on uterine blood flow. This study, therefore, was designed to determine the minimum effective concentration of epinephrine in cesarean section patients. Serum lidocaine levels, analgesic efficacy, and neonatal status were evaluated following epidural administration of a standard dose of 2% lidocaine with different concentrations of epinephrine.

Methods. Forty term parturients scheduled for elective cesarean section under epidural anesthesia were divided into four groups. Patients were randomly assigned to receive 20 ml of 2% lidocaine with epinephrine concentrations of either: 0 (plain); 1:400,000; 1:300,000; or 1:200,000. Solutions were freshly prepared and injected incrementally at the L3-4 level, via the needle, in a double-blind fashion. Supplemental analgesia was provided with 3% 2-chloroprocaine as necessary. Serum lidocaine concentrations were measured by radioimmunoassay (sensitivity + 0.02 ug/ml) in maternal blood sampled from a large antecubital vein at: 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, and 120 min following drug administration, and at delivery. Umbilical artery (UA) and vein (UV) lidocaine levels were measured in blood sampled from a doubly clamped segment of umbilical cord. Block characteristics were evaluated and side effects noted. Neonates were assessed using Apgar scores, cord blood gas analyses, and neurobehavioral testing (NACS) at 15 min, 2 h, and 24 h of age. The study was approved by the Institutional Review Board and informed consent was obtained from all subjects. Data were analyzed with Anova, Chi square, and Kruskal-Wallis tests as appropriate. A p value of <0.05 was considered significant.

Results. The groups were similar with respect to age, height, weight, and gestational age. There were no significant differences with respect to mean or peak maternal lidocaine concentrations, time to peak concentrations, UA and UV lidocaine concentrations, and UV/MV ratios at delivery (fig; table). Onset of block was faster with 1:400,000 and 1:300,000 epinephrine (4.5-4.7 \pm 0.5 min, mean \pm SEM) than with 1:200,000 epinephrine (6.5 \pm 0.7 min; p<0.05) or plain lidocaine (6.0 \pm 0.6 min). Patients in the plain lidocaine group required significantly more supplemental chloroprocaine (13 \pm 2 ml) to obtain adequate analgesia than did those in the epinephrine-containing groups (5-7 \pm 2 ml; p<0.05). The incidence of hypotension was similar and neonatal outcome was equally good in all groups.

<u>Discussion</u>. In the present study epinephrine did not decrease serum lidocaine levels, although it did improve analgesic efficacy. In non-pregnant patients, serum concentrations following administration of a standard dose of lidocaine were decreased

when epinephrine was added. 1 In pregnant patients, similarly decreased lidocaine levels have been reported with epinephrine; 2,3 however, smaller total doses of lidocaine were administered to patients who received epinephrine-containing rather than plain solutions, probably reflecting better analgesia with the former mixtures. The failure of epinephrine to reduce lidocaine concentrations in the current study may be due to decreased responsiveness to vasocon-strictors during pregnancy. It is not clear why analgesia was improved with epinephrine. However, it may be due to an anti-nociceptive effect mediated by alpha2-adrenergic stimulation at a spinal level. Our data suggest that maternal and fetal toxicity is unlikely to occur with 20 ml of 2% lidocaine and that epinephrine concentrations need not exceed 1:300,000 to 1:400,000.

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Fig. Mean Serum Lidocalne Concentration (± SEM)

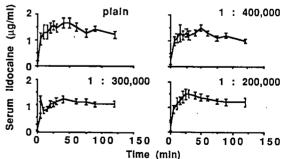


Table		(,	
Table	Time to peak concentration (min)	Peak lidocaine concentration (µg/ml)	UV/MV
Plain	43 ± 7	1.97±0.2	
1:400,000	33 ± 4	1.87±0.3	0.68±0.05
1:300,000	46 ± 7	1.43±0,4	0.80±0.09
1:200,000	32 ± 6	1.73±0.2	0.61±0.08/
Values are Me	an ± SEM	See	N. The state of th

OXYGEN SATURATION IN POST-CESAREAN PATIENTS USING EPIDURAL MORPHINE, PCA, OR IM NARCOTIC ANALGESIA

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Introduction. Epidural narcotics and patient controlled analgesia (PCA) are said to be superior to IM narcotics for the relief of postoperative pain. Although all three techniques can result in impaired responsiveness to CO2, their propensity for causing clinically significant hypoxemia has not been adequately investigated. In a recent study of oxygen saturation (SaO₂) following epidural morphine and IM narcotics, Choi et al. 1 documented brief periods of desaturation, but no significant differences between the groups. In that study, 1 however, the low alarm on the oximeter was set at 85%, which might have foreshortened periods of severe desaturation by arousing the patient and thereby stimulating respiration. Since we were not aware of studies reporting SaO2 following PCA, the current study was designed to compare the incidence and severity of desaturation episodes in post-cesarean section patients following epidural morphine, PCA, or IM narcotic analgesia.

The study population consisted of healthy, non-obese, term parturients who had undergone elective cesarean section with lidocaine or bupivacaine epidural anesthesia. For postoperative analgesia, patients received either: epidural morphine, 5 mg, (n=21); PCA meperidine via the Abbott Lifecare PCA Infusor (n=16); or IM meperidine (n=6). The latter two treatments were administered according to the usual regimens prescribed in the institution. SaO2 was measured for the first 24 h after operation with a Nellcor N-100 pulse oximeter (with the alarm inactivated) using a sensor taped to the patient's toe. In addition, respiration was monitored intermittently by a nurse according to routine hospital protocols. No patient received supplemental oxygen. SaO₂ data were collected and stored continuously (except when the patient was ambulant) via an interface connected to a Compaq computer. Desaturation episodes (defined as lasting at least 30 sec) were identified after carefully eliminating artifacts. For analysis purposes SaO₂ was divided into five categories: 95-100%, 90-95%, 85-90%, 80-85% and <80%. The total time of monitoring, the cumulative time in each category, the number and duration of desaturations, and the minimum SaO_2 were recorded for each patient. Data were analyzed using one way ANOVA, Kruskal Wallis, and Chi-Square tests as appropriate. The study was approved by the Institutional Review Board and written informed consent was obtained from all participants.

Results. The groups were similar with respect to age $(30 \pm 2 - 33 \pm 1)$ yr; mean \pm SEM), height $(163 \pm 1 - 165 \pm 5)$ cm), weight $(70 \pm 2 - 75 \pm 3)$ kg), and total time monitored per patient $(958 \pm 45 - 1105 \pm 89)$ min). SaO₂ was above 95% for the majority of the monitored period (table 1). However, patients in all groups spent a considerable proportion of the time with SaO₂ at 90-95%, with PCA patients spending the most time in this category (p <0.05 PCA vs. epidural). Briefer periods were spent with SaO₂ less than 90%, with no significant differences among the groups (table 1). Episodes of desaturation to less than 85% were common in all groups (table 2). The

mean minimum SaO_2 was lowest in the epidural group [p <0.05 epidural vs. PCA; table 2). The lowest individual SaO_2 recorded in each group was: epidural - 65%; PCA - 75%; and IM - 81%. Severe and prolonged desaturations occurred in one patient in each of the epidural and the PCA groups (SaO_2 <85% for 3.5 min, and 2.5 min, respectively).

Discussion. These data demonstrate decreases in saturation with all three analgesic regimens. Mild desaturation existed for about 25% of the monitored period with PCA, whereas shorter periods of more severe desaturation occurred with epidural morphine. Our results do not support adopting unique respiratory monitoring protocols for patients receiving epidural narcotics. Rather, they suggest that all patients should undergo more intensive surveillance in the first 24 h postoperatively. An alternative hypothesis is that our data, although accurate, may not reliably predict outcome. We believe that informed decisions regarding appropriate monitoring practices must await the results of large scale studies of the morbidity and mortality associated with these newer techniques.

Reference.

Choi HJ, Little MS, Fujita RA, Garber SZ, Tremper KK. Anesthesiology 1986; 65:A371.

Table 1.

Cumulative time (min) with SaO2 at	EP! (n=21)	PCA (n=16)	IM (n=6)	
95-100%	838±60	773±82	979±120	
90-95%	112±30	254±56*	127±50	
85-90%	5±3	12±8	0.3±0.3	
83-85%	0.5 ± 0.2	0.3±0.3	0 ± 0	
≤ 80%	1.0±0.6	0 ± 0	0 ± 0	

Mean± SEM

* p<0.05 vs. EPI

Table 2

Table 2.	EPI	PCA] ім
	(n=21)	(n=16)	(n=6)
Number (%) of patients with desaturation episodes ≤85%	15 (71%)	4 (25%)	5 (83%)
No. of episodes per patient (to ≤85%)† (range)	3±1 (1 - 14)	2±2 (1 - 35)	1±1 (1 - 4)
Minimum SaO2% †	83±2*	89±1	86±2

† Mean ± SEM

* p<0.05 vs. PCA

RAPID SEQUENCE INDUCTION OF ANESTHESIA FOR CORONARY ARTERY BYPASS SURGERY: ETCMIDATE VERSUS Title:

SUFENTANTI.

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<u>Introduction</u>. Patients at risk for aspiration pneumonitis often present for coronary artery bypass grafting (CABG). In this circumstance, a safe, simple, rapid sequence induction technique incorporating succinylcholine (SC) would minimize the time between loss of consciousness (when the patient's airway is unprotected) and tracheal intubation.

Both etomidate (E) and sufentanil (S) minimally depress cardiovascular function in critically ill patients (1-3). In this study, we compare the hemodynamic and electrocardiographic consequences of anesthesia induction (and intubation) with E or S and SC in randomly-assigned, elective CABG patients.

randomly assigned to receive either E (014 mg·kg) or S (5 mcg·kg) with SC (1 mg·kg) i.v. for induction of anesthesia. To prevent skewing of data, patient exclusion criteria included: ejection fraction (EF) < 40%, age < 18, pregnancy, medical conditions contraindicating any of the study drugs (e.g., malignant hyperpyrexia susceptibility), myocardial infarction within 7 days, or the need for a pacemaker or a vasoactive drug infusion prior to induction of anesthesia.

Ninetv minutes after standard morphine/anxiolytic premedication, patients were brought to the operating room for placement of i.v. and radial artery cannulae, as well as a thermodilution pulmonary artery catheter. Fluid was infused i.v. to raise the pulmonary artery diastolic pressure to \geq 10 mm Hg prior to induction. Following baseline measurement of systemic arterial, pulmonary arterial and central venous pressures, and cardiac output, continuous strip chart recording of ECG leads II and $\rm V_{\rm p}$ began. Oxygen was administered by face mask for 3 min., all measurements were repeated immediately prior to intubation which occurred exactly 1 min following induction with either E or S and SC, then again 3 and 6 min following induction. If heart rate were \geq 95 or \leq 40, MAP rose or fell by 50% or more, or ST segments rose or fell > 1 mm in any lead (at any time following induction), we administered metoprolol, atropine, nitroprusside, phenylephrine, or nitroglycerin, respectively. The combination of tachycardia and hypertension resulting from "light" anesthesia was treated with incremental doses of S (1 mcg - kg-1). Anesthesia in all patients was maintained (after the study) with up to 10 mcg·kg S (total cumulative dose) S supplemented with metocurine/pancuronium and lorazepam (up to 2 mg i.v.).

A cardiologist (RLR), unaware of the patient's treatment group evaluated all ECG tracings. Significance of results was assessed using paired t-test, analysis of variance, or Fisher's exact test, where appropriate.

Results. The two treatment groups did not differ in regard to: age, sex, LVEDP, EF, pre-

operative treatment with beta or calcium channel blockers, or baseline hemodynamic measurements. Following induction, mean hemodynamic values again did not differ significantly between the 2 groups at the time periods reported (Table 1). However, 8 of 9 E patients required drug intervention (following the protocol described above) - usually immediately following intubation - whereas only one of 11 S patients required treatment with an additional drug (p < 0.001). In addition, 3 of 9 E patients showed new ST - segment signs of ischemia whereas none of 11 S patients in this study (p = 0.07) (or 7 others identically managed in a companion study) had new evidence of ischemia. No patient in either group showed new q-wave signs of an infarct on postoperative, 12 lead ECGs. One (E) patient had vague recollections of intraoperative noises; no other patient recalled intraoperative events.

Any induction technique used Discussion. during open heart surgery should have favorable hemodynamic effects, should have a minimal number of predictable side effects, and should not induce ischemia. Additionally, the care of patients at risk for pulmonary aspiration of gastric contents is compromised when the anesthetist must divert his attention from the airway to manage unexpected, adverse hemodynamic and electrographic complications. S unlike E produced predictably favorable hemodynamic values when combined with SC for rapid sequence induction. While both drug combinations produced acceptable mean hemodynamic values at the time periods reported, the combination of E with SC required so much ill-timed "fine tuning" that we cannot recommend its use for similar patients. Moreover, we felt ethically bound to stop randomizing patients to that drug combination after reviewing these results.

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Table 1. HEMODYNAMIC RESPONSE TO RAPID SEQUENCE INDUCTION

	GROUP	BASELINE	1 min	3 min	6 min
MAP	E	95(14)	86(25)	101(43),	81(14)
(mmHg)	S	98(17)	82(11)+	86(12)+	90(12)
HR	E	68(17)	77(21)	79(20)	68(16)
(mmHg)	S	59(11)	60(14)	61(12)	61(14)
CO	E	5.8(1.0)	6.1(1.1)	6.6(1.9)	5.5(1.1)
(L/min)	<u>s</u>	4.8(1.2)	4.6(1.2)	5.0(1.5)	5.1(1.6)
PCW	E	13(4)	15(6)	15(11)	14(7)
(mmHg)	S	13(3)	14(4)	13(4)	14(4)
Mean (S	SD)	-			

p < 0.05 compared with control values

Title: SPREAD OF EPIDURAL ANESTHESIA IN PREGNANCY: CAN EPINEPHRINE CONTRIBUTE TO THE CONTROVERSY?

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INTRODUCTION: Spread of local anesthetic solutions in pregnant women undergoing epidural anesthesia is controversial. Exaggerated spread as compared to non-pregnant patients has been described by authors(1,2) using local anesthetic associated with epinephrine 1:200,000, while no such difference has been noted by authors using plain solutions (3). It is our impression that epinephrine could contribute to this controversy.

METHODS: The Clinical Research Committee approved the protocol. 0.75% or 0.5% bupivacaine, in the fixed dose of 150 mg, containing or not epinephrine 1:200,000, were injected at a rate of 1 ml/s via a 15 gauge Tuohy needle into the epidural space of 156 pregnant (cesarean sections) and of 156 non-pregnant (gynecological operations) patients under 40 years of age. Injections were performed at L2-L3 to L4-L5 interspaces with patients in the sitting position. All patients were placed supine, with manual left iterine displacement in the pregnant group. Thirty to fourty minutes after injection, anesthesia levels vere determined by absence of pain to pinprick, tested in the midclavicular line on both sides. Total number of blocked segments included 5 sacral, 5 lumbar and a variable number of thoracic dermatomes. Data were compared with Student's t-test for unpaired samples.

RESULTS: Age, height and weight (pre-pregnancy for the pregnant group) were similar in all groups (Table I). Total number of spinal segments were similar for the pregnant and non-pregnant patients receiving 0.5% and 0.75% burivacaine plain. More extensive epidural anesthesia was observed in pregnant patients, however, when 0.5% and 0.75% bupivacaine were associated with epinephrine 1:200,000 (p≤0,01). DISCUSSION: In previous work, epinephrine 1:200,000, out not 1:400,000, has shown to increase 0.75% bupiracaine spread in the epidural space of patients indergoing cesarean section (4), probably related to 1 reduction in the total amount of drug transferred to the central compartment (5). The present results further reinforce the important role of epinephrine luring pregnancy. An increased spread of anesthesia vas demonstrated in the pregnant group only when).5% or 0.75% bupivacaine were associated with epimephrine 1:200,000. It is our opinion that epinephrine has to be considered as a factor that can affect physical spread of local anesthetics within the epidural space, specially during pregnancy and that, it could contribute to the above mentioned controversy. We also believe that although these lifferences were observed, the recommendation for reducing the epidural dose of local anesthetic in the pregnant patients when compared to non-pregnant patients could lead to unsucessful clinical anesthesia.

Table I

Bupi- vac.	N	G	Weight (kg)	Height (m)	Age (yr)	Spinal Segments Blocked
.50%P	24	N	55.5+9.0	1.54+.06	31.6+5.8	16.7+2.0
.50%P	24	Y	57.7+11.7	1.63+.06	27.8+4.1	17.2+1.6 N.S.
.50%E	44	N	56.1+9.3	1.58+.07	32.9+5.9	16.3+1.5
.50%E	44	Y	56.3+9.5	1.59+.06	31.7+3.5	17.7+2.0 *
			56.8+8.0	1.61+.06	30.7+4.8	16.4+2.0
.75%P	18	Y	61.0+10.0	1.61+.05	31.2+4.6	17.0+1.2 N.S.
.75%E	70	N	57.9+9.3	1.59+0.7	32.9+6.4	17.1+2.0
.75%E	70	Y	57.2+8.7	1.61+.06	30.9+3.9	18.2+1.5 *

N= number of patients; G= gestation (N=NO, Y=YES)
P= plain; E= epinephrine 1:200,000.
N.S.= nor significant * p<0.01

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Title: INTRAVENOUS MEPERIDINE FOR CONTROL OF SHIVERING DURING EMERGENCY CESAREAN SECTION

UNDER EPIDURAL ANESTHESIA.

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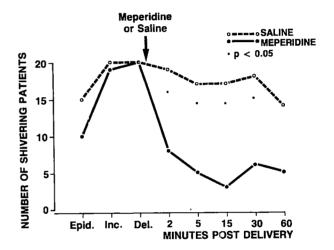
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INTRODUCTION:
complication of epidural anesthesia. This symptom is distressing to the patient, interferes with monitoring devices and significantly increases oxygen consumption and cardiac output. Intravenous meperidine has been successfully employed to treat shivering following general anesthesia, amphothericin chemotherapy and post cardiac surgery. The study was undertaken to evaluate the efficacy and safety of meperidine in controlling shivering during epidural anesthesia for cesarean (C) section.

METHODS: The Protocol was approved by the Hospital Ethics Committee. Informed consent was obtained from each patient. Studies were performed in 40 patients requiring emergency C-section under epidural anesthesia. After placement of an epidural catheter at the L_{2-3} or L_{3-4} interspace and fluid loading with 1-2 litres of 0.9% saline, carbonated 2% lidocaine with 1:200,000 epinephrine was given epidurally to achieve an adequate block. Arterial pressure, EKG, oxygen saturation, respiratory rate and membrane temperature were monitored continuously. After delivery of the infant, shivering patients received a single dose of either intravenous meperidine 50 mg (n=20) or 0.9% saline (n=20) in a randomized double blind fashion. Shivering was classified as O=none, 1=mild but not distressing to the patient, 2=moderate and distressing, 3=severe and distressing and interferring with monitoring. Potential side-effects such as drowsiness, nausea or diminished respiration were carefully noted. Shivering and other parameters were recorded at epidural placement, skin incision, delivery and at 2, 5, 15, 30 and 60 minutes following injection of meperidine or saline. Data were analyzed by chi-square with Yates correction for continuity, Spearmans rank correlation and student's "t"

RESULTS: The groups were similar with respect to age, number of primigravidae, indication for C-section, duration of labor prior to surgery, total fluid received, dose of lidocaine and level of block, although the saline group weighed less than the meperidine group (69 + 2 vs. 78 + 3 kg, p < .05). At delivery, all patients in both groups (100%) were shivering the majority being classified as severe (63%). The administration of meperidine resulted in a significant decrease in the incidence (p < 0.005) and severity (p < 0.001) of shivering compared with saline. This effect was apparent within 2 minutes and persisted throughout the study period (Figure). There were no significant differences in arterial

pressure, heart rate, oxygen saturation, respiratory rate or temperature between the two groups. The incidence of nausea was similar between groups (15-30%). Patients receiving meperidine were significantly more drowsy at 2 and 5 minutes following injection (X 2 =6.5, p < 0.005) although there were no differences in levels of consciousness between groups at the later intervals.



DISCUSSION: The study documents the successful treatment of shivering during epidural anesthesia in patients undergoing emergency C-section. Previous attempts to decrease the incidence of shivering have focused on warming the intravenous fluids, warming the epidural local anesthetics, or applying radiant heat to the upper chest. The mechanism of action of meperidine may be via information in the brain, spinal cord or rexed laminae, mediated through one or more of the recognized subpopulations of opioid receptors.

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RESPIRATORY MONITORING FOR POSTOPERATIVE PATIENTS RECEIVING EPIDURAL OPIOIDS

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Introduction. Epidural opioid administration is an accepted mode of therapy for postoperative pain relief. With any type of epidural opioid there is a possibility of respiratory depression. In this study we investigated the usefulness of the pulse oximeter and end-tidal CO2 monitor as indicators of respiratory depression.

Methods. Following approval from the Institutional Human Subjects Committee, informed consent was obtained from 15 patients scheduled for intraabdominal surgery. None of the patients had significant cardiopulmonary, hepatic, or renal disease. Preoperative medication was diazepam 5-10 mg. A lumbar epidural catheter was placed preoperatively and a sensory block between T4 and T7 was established prior to induction with lidocaine 1.5% or bupivicaine 0.5%. All patients had general endotracheal anesthesia induced with thiopental 3-5 mg/ kg and succinylcholine 1-2 mg/kg. Light general anesthesia was maintained with 50-70% NO2 and isoflurane 0.25-0.75%. Intraoperatively if the patient became tachycardic and hypertensive from surgical stimulation 5-10 ml of lidocaine 1.5% or bupivicaine 0.5% was given epidurally. After surgery each patient was extubated and monitored in the postanesthetic care unit. Oxygen saturation (SpO2) was measured by a finger probe from the pulse oximeter (501+, Criticare Systems, Inc.). End-tidal CO2 (PetCO2) and respiratory rate (RR) were monitored by a nasal cannula which aspirated exhaled breath for measurement (Lifespan 100, Biochem). Sp02, Pet CO2, and RR were continuously recorded on a Gould 4channel strip chart recorder. When the epidural blockade receded, resulting in a pain visual analog score (VAS) of 3 or greater on a scale of 0-10, epidural sufentanil was started. A sufentanil bolus of 0.3 mcg/kg mixed to a volume of 8 mls was given, followed by a continuous infusion of sufentanil, 0.3 mcg/kg/hr at 8 ml/hr. Ten minutes following the initial bolus of sufentanil a VAS score > 3 resulted in an additional bolus and increasing the infusion rate by 50%. This was repeated until VAS was \le 3 or RR < 10. The study period lasted 8 hours, VAS was recorded at ten minute intervals until stabilized, and then at hourly intervals following initial bolus. The epidural infusion rate was also tracked for 8 hours. The correlation of hourly changes of RR was compared to hourly changes in Sp02 and PetC02 by Spearman rank correlation. Correlation was significant when p < 0.05.

Results. There were 8 females and 7 males whose mean age was 50.1 years (range 20-77). The overall sufentanil infusion rate was 0.36 mcg/kg/hr. The initial VAS mean was 6.11 (range 3-10) prior to first bolus, a rapid onset of analgesia was noted at 10 minutes with a decrease in mean scores to 2.33 (range 0-8). The mean hourly data are shown in Table 1. Several patients were asleep at scheduled measurement intervals and were assigned a score of 1. Eleven patients needed another bolus with an increase in infusion rate. In patients breathing room air correlation between RR and PetCO2 (r=0.23) was statistically significant. There were no significant correlation between RR and Sp02 (r=0.07) or PetC02 & Sp02 (r=0.01). In patients who received supplemental oxygen there were no significant correlation between changes in RR and PetCO2 (0.01), RR and Sp02 (r=0.04) or PetCO2 and SpO2 (r=0.0). During the study period there were 4 episodes of Sp02 < 90%, one having a RR < 10. All these patients were breathing room air and were subsequently started on supplemental oxygen. There were 3 patients with PetCO2 > 50 but none had a RR < 10.

<u>Discussion</u>. In this study as respiratory rate changed there was corresponding changes in PetCO2 when patients are breathing room air. When patients are on supplemental oxygen this correlation no longer exists. This may be due to reduction in hypoxic drive and changes in V/Q matching. Pulse oximetry was useful detecting Sp02 < 90% in several patients but there was no correlation with RR when patients were breathing room air or on supplemental oxygen. This lack of association may be attributed to the wide variation in PaO2 with only small changes in Sp02. This study indicates that end-tidal CO2 would be better than pulse oximetry in following respiratory rate in patients receiving postoperative analgesia with epidural sufentanil. However, pulse oximetry would be a useful adjunct in evaluating the patients respiratory status.

<u>Table 1</u>

Hour	base		2	. 3	4	5	. 6	7	8
RR	18.9	15	16.1	15.4	16.1	17.2	15.9	15.9	15.3
ŞEM	1.44	0.93	0.95	0.96	0.97	0.66	0.85	1.00	0.84
Sp02	97.1	95	96.2	95.3	94.3	95.1	95.3	95.6	95.2
SEM	0.78	1,00	0.84	0.92	0,89	1.08	0.77	0.77	0,80
Pet CO2	34.7	39.4	38.9	39.9	39.3	39.8	38.4	37.8	39.1
SEM	1.48	1.88	2.44	2.36	2.02_	1,95	2.12	1.92	1.91
VAS	6.11	1.15	1.49	2.63	2.27	2.22	2.34	3.04	2.41
SEM	0.65	0.40	0.49	0.72	0.56	0.56	0.48	0.73	0.53

Title.

ISOFLURANE VS SUFENTANIL FOR CABG SURGERY

Authors:

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Introduction. The ideal anesthetic for patients with coronary artery disease has yet to be determined. The question of the role of volatile versus narcotic based anesthesia persists1. We undertook this study to compare sufentanil (SUF) in two dose regimens to isoflurane (ISO) with regards to hemodynamic stability, the incidence of perioperative ischemia, and the need for pharmacologic intervention.

Materials and Methods. Twenty-six patients with ejection fractions > 39%, and without valvular lesions scheduled for CABG surgery were randomly assigned to one of 3 groups after obtaining informed consent. Premedication in all groups consisted of morphine 0.15 mg/kg and lorazepam 0.04 mg/kg IM 90 minutes prior to surgery. Group I received 25 mcg/kg SUF at induction and no further scheduled dosing. Group II received SUF 4 mcg/kg at induction, and one minute prior to incision and pericardiotomy. Group III received diazepam, 0.3 mg/kg for induction and maintenance with 50% N₂0/O₂ and ISO 0.5-3%. Muscle relaxation was achieved with pancuronium 0.04 mg/kg and metocurine 0.12 mg/kg IV at induction and at institution of CPB in all three groups. Prior to induction a continuous (Holter leads II, V5) and 7 lead EKG, 20 g radial artery and PA thermodilution catheter were placed. Standard hemodynamic variables (and derived indices) were recorded at the following times: (1) awake (AW), one minute post (2) induction (IND), (3) intubation (INT), (4) skin incision (INC), (5) sternotomy (STER), (6) pericardiotomy (PER), and (7) aortic dissection (AoD). Alterations in hemodynamics were treated as in Table I ("interventions").

Holter tapes were evaluated by a cardiologist unaware of the patient grouping. Significant ST depression or elevation was defined as more than 0.1 mV amplitude and lasting more than 0.3 MI was defined as new persistent Q waves or T wave inversion. Statistical analysis was carried out using MANOVA corrected to baseline (awake) values and Chi Square as appropriate.

Results. Preoperatively, the groups were comparable in all hemodynamic and demographic variables with the exception of baseline SVR, which was higher in group III. There were no significant differences in any measured variables between groups I and II, hence, they were combined to form a SUF group for comparison with the ISO group. The prebypass period showed significant differences (Table II) between SUF and ISO groups only in HR (higher in ISO at INT and PER, lower at AoD), and CI (lower in ISO at INC, STER, PER, and AoD). Pharmacologic interventions averaged 4.2/pt in the SUF group and 3.5/pt in the ISO group. Most (65%) interventions were at PER or AoD in the SUF groups. whereas interventions in the ISO group occurred early (63% at INT, INC, or STER).

ST segment depression was noted on Holter analysis in 4 of 17 SUF patients and 4 of 9 ISO patients. This was recognized in the OR in only two patients. One patient (ISO group) who showed no evidence of ischemia in the OR had a perioperative MI. No deaths ensued.

Discussion. Our data show that ISO without supplemental narcotics does, indeed, increase HR and decrease CD when compared to a "pure" narcotic technique. We identified ischemia restrospectively in 31% of our patients (a rate consistent with other reports in the literature 2) but identified it intraoperatively in only 8% despite meticulous attention to the electrocardiogram. We saw no significant differences in the incidence of intraoperative ischemia or perioperative MI, nor did either technique have a clear advantage as measured by the necessity for pharmacologic intervention. However, those interventions may be needed earlier (when anesthesia is light) with a volatile agent and later (as the narcotic redistributes) in a narcotic technique.

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Table I Treatment of Herodynamics

	Groups I and II	Group III	Secondary Treatment				
Hypertension (BPS>140)	SUF 1 mcg/kg X 2	Increase ISO	TNG, SNP				
Hypotension (BPS<90)	Vasopressors as needed						
Tachycardia (HR>90)	Propanolol 0.5 mg until HR <90						
Ischemia (ST decreased, new V wave)	TNG, or Vasopressors (if hypotensiv	e) + TNG				

Table II. Corporison of Herodynesic Pessurements Between Suferitanii (Groups 1 and III) and Isoflorame (Group IIII)

	,	w	P	•0		INT		ж	5	TER	FEDR	AdD .
	SJF	150	937	1 150	9F	IS0_	<u> य</u>	150	935	193	SE 150	या छ
589	163+23	151+26	119+23	112+21	127+21	125421	122+15	103+12	132+50	171+75	144+24 126+15	122+23 \$F+15
HR	63+9	66+8	€3+9	72+11	64-6	80+8	93+7	55+ 10	57+7	⊕IJ	57-6 * X0-14	67+12 + 59+9
SVR	1753+526	1331+225	1311+357	:157+290	1397+399	1303+363	1569+352	1391+228	1650+355	1477+3CE	1747+05 1572+287	1691+478 1260+274
Ct	2.5+.6	2.8+.6	2.4+.7	2.5+.5	2.4+.6	Z.6+.4	Z.0×.4	* 1.9+.2	2.1+.4	ć.+1.5 •	2,24,4 * 2,14,4	2.2+.4 + 2.0+.2
*p×0.	*pXX.05 by MMXXA as concurred to smale basel fire											

POST-ANESTHETIC VOMITING IN CHILDREN UNDERGOING STRABISMUS REPAIR: A COMPARISON OF DROPERIDOL AND LIDOCAINE

Authors:

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Introduction: Droperidol (0.075 mg/kg) has been shown to decrease the incidence of vomiting after strabismus repair from 60% (controls) to 16%. Despite the effectiveness of droperidol in this regard, it is used reluctantly in outpatients because of its prolonged sedative effect which may delay discharge from hospital. Recently, lidocaine was shown to attenuate the ocular reflex responses to intubation² and reduce the incidence of vomiting after strabismus repair from 52% to 20%.3 Therefore, we compared the effects of droperidol and lidocaine on the incidence of vomiting and the duration of drowsiness after strabismus repair in children.

Methods: With approval from the local Human Review Committee, a prospective randomized double-blinded study was undertaken. Informed written consent was obtained from the parents of 150 children scheduled for elective strabismus repair. The patients were all ASA I or II, fasting, and unpremedicated. The children were anesthetized with intravenous thiopental (5 mg/kg), atropine (0.02 mg/kg) and succinylcholine (2 mg/kg), the tracheas intubated and the lungs ventilated with halothane, nitrous oxide and oxygen. The children were randomized to receive one of three treatments at induction of anesthesia: Group A droperidol (0.075 mg/kg) intravenously, Group B lidocaine (1.5 mg/kg) intravenously infused over 30 seconds, and Group C droperidol (0.025 mg/kg) intravenously and lidocaine (1.5 mg/kg) infused slowly over 30 seconds. The stomachs were not aspirated. Postoperative pain was treated with oral or rectal acetaminophen 10 mg/kg. Each patient received an intravenous with D5/0.25%S to replace the estimated fluid deficits and ongoing maintenance requirements.

The nurses in the recovery room (RR) and on the ward were blinded to the patient's treatment group. They recorded the time and frequency of all episodes of vomiting, treatment required, time to discharge from the RR and time to discharge from hospital. The parents of each child were contacted within several days after surgery to determine the incidence of vomiting at home.

The patient's age, weight, total incidence of vomiting (in hospital and at home), time in the RR and time to discharge from hospital were also recorded.

Statistical significance (p < 0.05) was determined using Chi-square analysis with the Yates correction for continuity for nominal data and the Bonferroni t-test for parametric data.

Results: Age and weight of the patients did not differ significantly among the three treatment groups (Table). The incidence of vomiting in Group B (50%) was significantly greater than Group A

(22%) (p < 0.05) (Table). The incidence of vomiting for patients in Group C (30%) did not differ significantly from either Groups A or B. The time in the RR was significantly shorter for Group B than for Group A and not different from Group C. The time to discharge from hospital did not differ significantly among the three groups.

Discussion: The results of this study indicate that droperidol 0.075 mg/kg is significantly more effective than lidocaine 1.5 mg/kg in preventing post-anesthetic vomiting. Although the sedative effect of droperidol may account for the delayed discharge of Group A from the RR, this effect did not delay their discharge from the hospital. We conclude that droperidol 0.075 mg/kg remains the optimal prophylactic measure to prevent vomiting after strabismus repair in children.

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TABLE

	GROUP A	GROUP B	GROUP C
Number of Patients	50	50	50
Age (yrs)	4.9	5.0	5.5
	<u>+</u> 2.07	<u>+</u> 2.23	<u>+</u> 2.29
Weight (kg)	18.5	19.3	21.2
	<u>+</u> 6.8	<u>+</u> '6:6	<u>+</u> 7.4
Incidence of vomiting	11/50	25/50 *	15/50
	(22 %)	(50 %)	(30%)
Time in RR (hr)	1.18	1.02*	1.11
	<u>+</u> 0.41	+ 0.24	<u>+</u> 0.31
Time to discharge (hr)	4.59	4.80	4.73
	<u>+</u> 0.94	<u>+</u> 1.27	<u>+</u> 1.08

Data are mean + S.D.

^{*} p < 0.05 compared to Group A

Title: A COMPARATIVE STUDY OF BACTERIAL CONTAMINATION OF REUSABLE AND DISPOSABLE SODA LIME ABSORBERS

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Introduction. According to a 1978 report issued by the Centers for Disease Control, pulmonary infections constitute approximately 15% of all nosocomial infections in hospitals (1). Anesthesia causes disturbances in normal ventilatory function including changes in respiratory epithelium which, theoretically, may lead to increased susceptibility to colonization by microorganisms. The role of the anesthesia machine as a source of microorganisms causing postoperative pulmonary infection has been a source of controversy in the anesthesia community for many years. This study was designed to examine whether circuits with sterile disposable absorbers (DSA) were at lower risk for contamination than circuits with reusable absorbers (RSA).

Methods. In a prospective, randomized study, the incidence of bacterial contamination of anesthesia machine breathing circuits containing DSA or RSA was compared. Eighty two patients (pts) undergoing operations in two different operating rooms of a major medical center over a period of six weeks were assigned randomly to receive anesthesia through circuits containing RSA or to those containing single use DSA cannisters. Permanent components of the circuit on the machine were cultured before each case. For circuits with an RSA, this included inspiratory and expiratory valve leaflets and ports, reservoir bag port, fresh gas flow inlet, and the rubber hose connecting the ventilator to the machine. For circuits with DSA, this included only the fresh gas flow inlet and the ventilator hose. After each case, cultures were obtained from the circuits. Swab cultures were taken from each end of the corrugated tubing. The internal surfaces of the tubing were cultured using a broth flush technique. The DSA were cultured by adding sterile water and broth, incubating for 48 hours, and subculturing the broth. Chemically inactive soda lime from the RSA was cultured in similar fashion. To determine whether microorganisms that contaminated the soda lime could be recovered by our culture technique, the DSA were spiked with gram positive and gram negative bacteria and cultures were performed as described above.

Results. Eighty two anesthesia circuits were randomized. Two were eliminated because they were accidentally discarded before final cultures were obtained. Thirty four (42.5%) of the circuits were in the DSA group and 46 (57.5%) were in the RSA group. Both groups of pts were similar in age, sex and race distribution, type of surgery and anesthetic, receipt

of intraoperative antibiotics, and presence of infection at remote sites. A total of 36 positive cultures were obtained. There were 16 (47.1%) in the DSA group and 20 (43.5%) in the RSA group. This was not statistically significant at a p < 0.05 level. Three anesthesia circuits were positive for microorganisms considered to be pathogenic; two were in the DSA group and one was in the RSA group. These microorganisms included Staphylococcus aureus (two) and Proteus mirabilis (one). This difference was not statistically significant at p < 0.05 level. All three pts had preoperative respiratory infections caused by these microorganisms. A total of 17 pts (21.25%) had infections at one or more sites prior to entrance into the study. Of the bacteria added to the DSA in the laboratory, only Staphylococcus aureus was recovered at 24 hours. However, no microorganisms were recovered at 48 or 96 hours.

Discussion. Albrecht and Dryden reported a rate of 23% for postoperative pulmonary infections in a retrospective review of pts over a period of five years using RSA. In a prospective review of postoperative pulmonary infections in pts on whom circuits with DSA were used, the rate of infection decreased to 5.7% (2). Our data did not support the observations of Albrecht and Dryden. We observed no significant difference in the rate of contamination between circuits containing DSA and RSA. Furthermore. there was no difference between circuits containing DSA and RSA and the rate of contamination with microorganisms considered pathogens. Indeed, pathogenic organisms were rarely isolated from either type or circuit. The health care field is increasingly subjected to pressure to reduce health care costs. Since the implementation of Diagnostic Related Groups reimbursement has been based on diagnosis, rather than actual patient costs. This study demonstrates that the use of DSA offers no more protection against contamination of circuits than does the use of RSA. Therefore, the increased cost of the DSA system does not appear justified.

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CALCIUM ANTAGONISTS IN AORTOCORONAR! BYPASS -- SHOULD WE BEWARE?

Authors:

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<u>Introduction</u>. Slogoff et al have recently demonstrated that in patients undergoing coronary artery bypass grafting (CABG) a significant relationship exists between tachycardia, myocardial ischaemia, and perioperative myocardial infarction (1). Their study did not show if the incidence of myocardial ischaemia is related to pre-operative cardiac medications. The aim of this study was to detect the difference in incidence of pre-bypass ischaemia by electrocardiogram (ECG) criteria in patients taking B adrenergic blockers (Group I), 2 channel blockers (Group II), or combined B adrenergic and Ca channel blockers (Group III).

Method. Institution approval was obtained. Patients with stable angina scheduled for routine coronary artery bypass grafts from January 1986 to March 1987 were included in the study. All cardiac medication was continued until the time of premedication. Calibrated ECG tracings of Lead I and V5 and haemodynamic profiles were recorded during the pre-bypass period and at the following intervals: before induction (baseline) and one minute after induction, intubation, skin incision. sternotomy, and aortic cannulation. A high dose Fentanyl anaesthetic protocol was used. Heart race (HR) and blood pressure (BP) were maintained with n 20 percent of the average ward value (control). For elevated BP, infusion of nitroglycerine with without the addition of an inhalational anaesthet_c up to 0.5% was used. For lowered BP, volume, and when necessary infusion of phenylnephine was given. For increased HR, intravenous doses of propranolowas used. ECG was examined retrospectively by two independent investigators for evidence of ischaemia. Ischaemia was defined as 1 mm or more of downsloping or horizontal ST segment depression greater than 2 mm of upsloping ST segment depression measured 0.08 seconds from the J-point. or ST elevation greater than 1 mm. Ischaemia, as evidenced by ECG changes, was analyzed according to the 3 groups of patients by analysis of variances, and haemodynamic data was analyzed by analysis of covariance using baseline as covariata. P < 0.05 was considered statistically significant.

Results. Ninty-two patients were studied: 23 in Group I (B-adrenergic blockers), 22 in Group I (Ca channel blockers) and 47 in Group III (B blockers and Ca blockers). There was no difference in age, weight, ASA class, severity of angina, LV score, ejection fraction, time of bypass or X clamp time among the three groups. The incidence of ischaemia (Fig. I) was significantly higher in Group II at induction (p<0.03), incision (p<0.05), and sternotomy (p<0.002). There was no difference in mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), or cardiac output (O) among the three groups at various stages prebypass. Heart rate at sternotomy was significant_ higher in Group II (p<0.02). Rate pressure product (Fig. II) was significantly higher in Group II at incision (p<0.05), sternotomy (p<0.0001), and cannulation (p<0.002).

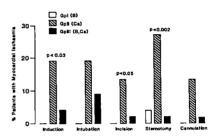


Fig. I % of Patients with Myocardial Ischaemia at Different Stages Prebypass

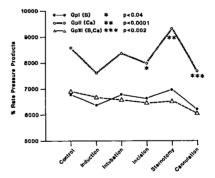


Fig. II Rate Pressure Product at Different Stages Prebypass

Discussion. The incidence of myocardial ischaemia at induction, incision and sternotomy was significantly higher in patients taking Ca channel blockers (Group II). The incidence of myocardial ischaemia in patients taking B adrenergic blockers (Group I), or combined B adrenergic blockers, and Ca channel blockers (Group III) were comparable, and were lower as compared to patients taking Ca channel blockers only (Group II). Patients taking Ca channel blockers, and with no B adrenergic blockade have a higher risk of developing prebypass ischaemia.

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PATIENT RECALL DECREASES IF A RISK-SPECIFIC ANESTHESIA CONSENT FORM IS NOT SEEN BEFORE

THE PRE-OPERATIVE INTERVIEW

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Introduction: In a previous study, we found decreased recall of anesthetic risks and increased anxiety if a risk-specific consent form was read with the patient during the pre-operative interview; giving patients the form at least two hours before the interview diminished these negative effects(1). However, we were concerned that these results might not apply to a general inpatient population because: a) one anesthesiologist conducted all interviews, b) all subjects were outpatients, and c) the form was read with the patient before it was discussed (an unlikely practice in a busy clinical setting). We undertook this study to determine the effects of a risk-specific consent form during routine inpatient use. Methods: We interviewed 125 adult inpatients before and 106 adult inpatients after our hospital required the use of separate anesthesia consent form in this IRB- approved study. Fourteen of the after-implementation patients received the consent form in a pre-admission packet 7 ± 4 days before admission and were considered separately from the other 92 patients. Residents completed demographic surveys and discussed five specific risks of anesthesia (death, paralysis, kidney damage, backache, damaged teeth) with each patient preoperatively. After this interview, we asked the patients to rank their anxiety on a four point scale. One of the authors interviewed each of the patients on the first postoperative day. Patients indicated the complications they remembered from a list of the five true anesthetic risks discussed pre-operatively and four false risks not discussed.

We used one way analysis of variance with Duncan's multiple range test to analyze both the recall data and the demographic data. P<0.05 indicated significance.

Results: Age, physical status, percent of patients having cancer-related surgery, anxiety level after the interview, educational level, and type of surgery did not differ among the groups. Ninety percent of all patients felt that they had received enough information about anesthetic risks.

Patients remembered fewer true anesthetic risks when they received the consent form during the preoperative interview than if they received it before the interview or not at all (P<0.01) (See Table 1).

Discussion: Our results extend previous findings (1) to an inpatient setting. Discussing the form during the interview had the same negative effect on recall as reading the form with the patient before discussing it. We also found no evidence of interviewer bias in that study, since we obtained similiar results with a large number of pre-operative interviewers. Although overall recall was lower in this study, Morgan found similar recall (37%) among cataract surgery patients. (2)

In summary, presenting a risk-specific anesthesia consent form during the preoperative interview adversely affects recall. Including the consent form in a pre-admission information packet prevents this decrease in recall.

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Table 1 - Patient Recall of Anesthetic Risks:

	Control	Patients received	
	(n=125)	During Interview (n=92)	Before Interview (n=14)
True Risks	33±3*	19 ± 3*	33±11
False Risks	10 <u>±</u> 2	6 ± 2	11 <u>+</u> 6

mean percent recall ± SEM

p<0.01 compared to control and before-interview groups.

Title: ASSESSMENT OF PATIENT SATISFACTION WITH ANESTHESIA SERVICES

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Introduction. The goals for the anesthesiologist include the afe conduct of anesthesia to facilitate surgical care, as well as to provide a satisfying experience for the patient. The quality of mesthesia care can be evaluated by systemic monitoring of morbility and mortality. The determinants of patient satisfaction are nore difficult to define and quantify. They probably vary from one attent to another and depend upon a number of factors over which he anesthesiologist has little control. To assess patient satisfaction with anesthesia services we conducted a survey of patient attitudes egarding anesthesia care provided in a teaching hospital with an mesthesia residency. The results of the survey were compared to hose from a similar survey of patients of community anesthesiologists.

Methods. A patient opinion survey was utilized to obtain infornation about patient satisfaction with anesthesia services.(1) The survey had three components: a) descriptive information about the vatient, b) patient opinions about their relationship with the nesthesiologist, and c) questions about access to information about nesthesia

After approval by the Committee on Human Research, surreys were mailed to 500 patients receiving anesthesia services from uly through September, 1985. The surveys were analyzed to comare patient satisfaction between residents in their first year of mesthesia training and those in their second year of anesthesia raining. In addition, the results were compared to a similar patient pinion survey for community anesthesiologists.(2) The data were malyzed using t tests, Chi square analysis, and multiple regression.

Results. Of the 500 surveys mailed, 255 (51%) were returned leven percent of the patients solicited formally refused to particitate and the remainder of patients solicited did not respond. Based upon the individual patient opinion items, over 80% of patients conidered explanations about anesthesia services and alternatives to be adequate. Fifty-five percent of patients indicated they would like nore information about anesthesia. Eighty-nine percent of patients expressed great confidence in the anesthesiologist. No significant lifterences were noted in responses between patients anesthetized by first (n=175) and second (n=80) year Anesthesia residents.

The responses to surveys of patients of the anesthesia esidents were then compared to those of the patients of 16 community anesthesiologists (n=257).(2) Patients who received nesthesia services in the teaching hospital, compared to those in the community sample were older, more often male, sicker, lesskely to have private insurance and more likely to have Medicare 37% vs 22%) or Medicaid (11% vs 3%) insurance coverage.

Factor analyses were performed, defining five scaleomprised of responses related to (1) explanations about nesthesia, (2) adequacy of information regarding anesthesia, (3] ommunication problems, (4) satisfaction with outcome, and (5] oncerns about cost.

The resident anesthesiologists were perceived by patients to ive better explanations about the proposed anesthesia, alternative and potential risks than community physicians (p < 0.05). No lifference was found between explanations provided by first and econd year residents. For both the resident and community nesthesiologists, the more educated patients were less satisfied with explanations and adequacy of information.

No differences were identified between resident and community anesthesiologists regarding problems with communication. However, those patients whose health improved after surgery reported fewer communication problems than those whose health did not improve. Older patients of both groups identified more communication problems with their anesthesiologists. Patients of community anesthesiologists were more pleased with outcome. They would more eagerly recommend their anesthesiologist to a friend.

The patients cared for in the teaching hospital were less concerned about cost than patients of community physicians. Despite the lack of concern, forty-seven percent of the patients of the teaching hospital and 41% of those cared for in the community hospital felt the cost of anesthesia services was more than anticipated. Patients of the community anesthesiologists desired more information about cost (28%) more often than those of the teaching hospital (17%) (p<0.05).

Discussion. The findings of this survey suggest that patients are interested in explanations about anesthesia services and information about potential complications. When such information is provided to them, however, patients do not necessarily indicate better satisfaction with anesthesia services. The perception of the quality of anesthesia services is apparently only partially dependent upon such explanations.

The discrepancy between adequacy of explanations and satisfaction with anesthesia services may be explained in a number of ways. Anesthesia residents who more effectively explain the anesthetic plan may spend more time with patients, providing detailed descriptions of the proposed anesthesia, alternatives, and risks. This disseminates information, and even instills confidence but does not necessarily translate into a satisfied patient. The discrepancy may be due to the difference in the age or level of experience of the anesthesiologists. The perception of satisfaction may also be dependent in part upon surgical outcome, since patients whose health improved postoperatively, more common for the community hospital patients, reported fewer communication problems and were more often satisfied with the anesthesia.

This study suggests that the interpersonal interaction between the patient and anesthesiologist is an important part of overall anesthesia care. In addition to the knowledge and technical skills required of the anesthesiologist, the relationship with the patient is a significant determinant of patient satisfaction. Other factors, out of the direct control of the anesthesiologist also play a role in patient perceptions of anesthesia care. Since patient satisfaction has obvious clinical and medicolegal significance, further study will be required to more clearly define the specific components of the interaction with the patient that facilitate a positive impression of anesthesia care.

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Title: A TWO CATHETER TECHNIQUE FOR RADIOGRAPHIC EVALUATION OF EPIDURAL SPACE

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Introduction. Presently, it is believed that chronic low-back pain syndromes are due to pathophysiologic changes causing mechanical pressure on nerve roots. Based on the assumption that inflammation is a major contributing factor to chronic pain, therapies with steroids administered epidurally were widely used since 1957 (1). The effectiveness of epidural steroids, however, has been seriously questioned (2). More recently, it has been reported that an epidural therapy, consisting of morphine and steroids, provides effective pain relief to a large percentage of patients presenting with chronic low-back pain (3). Here, with a two catheter technique, we radiographically evaluated the distribution of medication in the epidural space in order to establish whether or not there is a correlation between outcome of therapy and the spread of drugs.

Methods. Participating in the study were fifteen adults presenting with chronic low-back pain syndromes secondary to multiple surgical interventions on the spine, who, in accordance with institutional guidelines, signed an informed consent. Protocol included detailed history, physical examination, radiographic studies with either CAT scan or MRI, pre- and post-spinal mobility measurements, self-scoring of pain intensity using visual analog scale (VAS), fasting overnight, intravenous fluid therapy, monitoring (for 24 h in the intensive care unit) of ECG, heart rate, blood pressure, and respiration, insertion of two epidural catheters, one above the surgical site and the other, caudally. A lumbar epidurogram, using the dye iohexol (Omnipaque 240), permitted confirmation of proper placement of catheters and accurate viewing of epidural space. With patient in head-up position, Duramorph (4 mg/4 ml) was injected via each catheter which was then flushed with 8 ml of sterile normal saline. Sixty min later, methylprednisolone acetate (80 mg/2 ml) was injected via each catheter, which, after being flushed with 8 ml of sterile normal saline, was withdrawn. Onset of analgesia and untoward effects of morphine were recorded. Somnolence, puritus, nausea, vomiting, urinary retention were treated symptomatically; respiratory depression was the only ill effect mandatorily requiring reversal by naloxone. Evaluation of therapy outcome, one month later, consisted of physical examination, spinal mobility measurements, self-scoring of pain intensity with VAS; also recorded were any adjunct therapies.

Results. Radiographic studies of the epidural space revealed total and partial occlusion in 10 and five of the patients, respectively; in all 15 patients, iohexol failed to spread uniformly between the insertion sites of the two catheters. All 15 patients, however, reported effective analgesia subsequent to the epidural administration of Duramorph but analgetic onset was delayed from the usual 20 to 60 and up to 180 min; there was no noticeable change in either incidence or severity of the therapy-induced untoward effects. No patient experienced respiratory depression; a 20% fall in blood pressure occurred in one patient on a regimen of the beta blocker, propanolol. At time of follow-up examination, the five patients with documented partial occlusion of the epidural space reported pain relief ranging between 25 and 80%, improvements which were confirmed by both mobility measurements of flexion, extension, lateral bending, and rotation, and VAS self-scoring. The two latter testing methods also agreed with reports of complete therapeutic failure in seven and effective pain palliation in three of the ten patients with total occlusion of the epidural space.

Discussion. It is well accepted that, despite recent major radiographic advances, accurate diagnosis of chronic low-back pain syndromes is difficult if not impossible (4). Thus, as it is virtually impossible to select a uniform group of patients for study and comparison, here, each patient served as his/her own control. The two catheter technique has the dual advantages of providing a clear view of the epidural space and effectively increasing drug distribution in this anatomical structure. Our findings strongly suggest that outcome of the epidural therapy is contingent upon the medication reaching the proper target site(s) in the nervous system where pain is modulated.

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BEAGLE PUPPY MODEL OF THE NEONATAL BRAIN: EFFECT OF NITROUS OXIDE ON CEREBRAL

BLOOD FLOW AND METABOLISM

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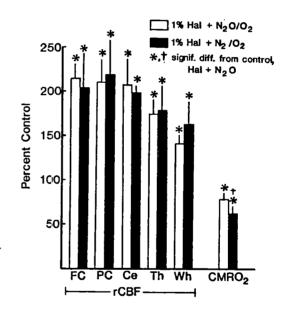
Introduction. Controversy exists over the effects of nitrous oxide on cerebral blood flow (CBF) and netabolism. In dogs nitrous oxide causes an increase im CBF and metabolism (1). In man, nitrous oxide mag ncrease CBF (2) or show no change (3). The effects or litrous oxide in newborns is unknown. The beagle puppy is used as a model of the neonatal brain (4). Using this mode. we looked at the interaction of nitrous oxide on CBF and CMRO2 with and without halothane anesthesia.

 $\underline{\text{Methods.}}$ Five pure bred beagle pups 2 to 6 days of age and 230 to 450 grams were anesthetized by mask with nalothane, nitrous oxide and oxygen, and tracheotomized. Following paralysis with intraperitoneal d-tubocurare, the oups were mechanically ventilated to maintain PaCO2 at 35-40 mmHg. Two femoral arterial and two femoral renous lines were placed for fluid administration, blood ressure and blood gas monitoring, and microsphere withdrawal. A catheter was advanced from the carotic artery into the left ventricle for injection of 15 um microspheres (57Co, 113Sn, 46Sc). A sagittal sinuatheter was placed for measurement of cerebral venous Do content. All incisions were made and catheters placed after local infiltration with 0.5% bupivacaine. Blood loss was replaced with maternal whole blood and mean arterial pressures maintained with epinephrine (1 ug/kg/min), if needed, following reintroduction of halothane (see below). Halothane was discontinued for 1 hour prior to beginning the study. Regional cerebral blood flow determinations and CMRO₂ were obtained during 70% N₂0/30% O₂. control), 7% halothane/70% N₂0/30% O₂, and 1% talothane/70% N₂/30% O₂. Regional cerebral blood flow rCBF) determinations were made for the frontal cortex. FC), parietal cortex (PC), cerebellum (Ce), thalamus (Th: and subcortical white matter (Wh) regions. CMRO2 was calculated from the average FC and PC rCBF and the ${\tt irterial}$ -sagittal venous ${\tt O}_2$ content difference.

Results. The results are expressed in Figure 1 as percent of control values (means ± SEM), and evaluated by malysis of variance. Data is presented for normotensive normocarbic animals only. Hemodynamically unstable pups were excluded from the study. There was a significant ncrease in rCBF to all regions with 1% halothane added to 70% $\rm N_2O$. With $\rm N_2O$ withdrawal, rCBF remained elevated. CMRO2 decreased with the addition of 1% nalothane to $\rm N_2O$. A further significant reduction in With N20 withdrawal, rCBF remained ${\rm CMRO_2}$ occurred with ${\rm N_2O}$ withdrawal, when compared to halothane/ ${\rm N_2O/O_2}$ (and ${\rm N_2O/O_2}$).

Discussion. The addition of 1% halothane to a 1/20/02 anesthetic causes a significant increase in rCBF and a reduction in metabolism. Although the effects of 120 on rCBF in this study were not compared to the

awake puppy, it is clear that the withdrawal of $\rm N_2O$ caused no change in rCBF. This suggests that any effect of $\rm N_2O$ on CBF is minor and not additive to the effect of halothane in puppies. Withdrawal of N₂O from halothane/N₂O/O₂ anesthetic causes a significant reduction in CMRO₂. N₂O appears to have a stimulating effect on cerebral metabolism in the presence of halothane anesthesia in puppies. This stimulating effect of N20 is also seen in adult dogs (1). However, this effect does not persist with 1% halothane in these older animals. An age related difference in the effect of N2O on cerebral metabolism is suggested by the present findings.



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Authors: Affiliation: SPINAL CORD INJURY: THE EFFECT OF SUBARACHNOID NALOXONE ON OUTCOME AFTER SPINAL CORD INJURY OCCURRING DURING NARCOTIC ANESTHESIA DJ Cole, M.D., JC Drummond, M.D., HM Shapiro, M.D., FS Brauer, M.D. Department of Anesthesiology, Loma Linda University, Loma Linda, Ca; Department of anesthesiology, University of California at San Diego, La Jolla, Ca.

Introduction: Narcotic antagonists have consistently demonstrated a protective effect against spinal cord injury. (1) This may have a profound effect upon the anesthetic decisions facing the anesthesiologist, as some have hypothesized that because narcotic antagonists are protectants, narcotic agonists may have a detrimental effect upon the extent of spinal cord injury. Thus, they would argue that narcotics should not be administered during a surgical procedure at

risk for spinal cord injury. In this study, we evaluated the effect of fentanyl (F) and naloxone (NX) upon neurologic outcome in the setting of spinal

cord injury.

Methods: Following approval by the Animal Research Committee, male, Sprague-Dawley rats (n=66) of similar weights (300-350 grams) were surgically prepared as follows: Day 1-placement of a subarachnoid catheter in the spinal canal with the tip at T_{8-9} . (2) Day 2-normal neurologic function was established, and a balloon tipped catheter was placed in the epidural space via a midline laminotomy at L_{2-3} with the balloon at the thoracolumbar junction. A tail artery catheter was inserted. This procedure lasted 30-45 minutes, and was followed by a 120 minute anesthetic recovery period during which normal neurological function was again established. Each rat was then randomly placed in one of the following groups: 1) Fentanyl/Nitrous Oxide-anesthesia was induced with fentanyl-57 ug/kg and 65% nitrous oxide $(\mbox{N}_2\mbox{O}),$ and each rat was orotracheally intubated and mechanically ventilated. Fifteen minutes after F administration the epidural balloon was inflated with a constant volume of air (0.1 ml) over randomly varying times (0, 6, 12, 24, or 42 minutes). Immediately after balloon deflation 20 ul of preservative free, pH buffered, saline was administered via the subarachnoid (SA) catheter. 2) Fentanyl/N₂O/NXanesthetic management was identical to group 1. The only exception was that instead of administering saline via the SA catheter, NX 1 mg/kg was administered via the SA catheter in a 20 ul volume that was pH matched to the other groups. 3) Awake-the spinal cord insult was administered while the rat was awake. Saline was administered immediately after the injury in an identical manner to group 1 and 2. Physiological parameters (CH, P. 20) cal parameters (pH, PaCO₂, PaO₂, mean arterial pressure, serum glucose, hematocrit, and temperature) were monitored.

Each rat was evaluated daily by a blinded investigator, for the presence or absence of hindlimb paralysis through 7 post-insult days. Statistical analysis was performed on the physiological data using analysis of variance and, as appropriate, mean values were compared by t-tests with a Bonferroni correction. Dose-response curves were constructed for post-insult day 7 data by plotting the duration of balloon inflation versus the percentage of paralyzed rats. The curves were statistically compared for slope and potency differences by group t-tests (P< 0.05).

Results: There were no significant differences in any of the physiological variables (P< 0.05). The dose-response curves are represented in Figure 1. There was a significant (P< 0.05) right shift in the curves for the F/N_2O and $F/N_2O/NX$ groups as compared

to the awake group. There was no significant difference between the curves for F/N_2O and $F/N_2O/NX$. This right shift demonstrates spinal cord protection by the anesthetic regimen of F/N_2O , with no additional protection afforded by NX.

Discussion: The protection demonstrated in this study may not be a unique property of fentanyl, but of anesthesia in general. The precise mechanism(s) whereby anesthesia protects against spinal cord injury are unknown, but may include favorable effects on the metabolic needs of the neuron. Other studies have demonstrated spinal cord protection by narcotic antagonists, in particular naloxone. These reports have not studied spinal cord injury in the context of anesthesia, as was done here, which may have a dramatic affect upon the overall pathophysio-In addition, naloxone was administered local to the injury and not systemically as has been done in previous studies. The local administration of NX was necessary to maintain the anesthetic state, however, it did eliminate systemic effects of NX which were present in other studies. Not only did the SA route of NX administration provide for maintenance of anesthesia, but should also provide for higher local tissue levels of NX.

The present study does not support the subarachnoid administration of NX following a spinal cord injury occurring during a narcotic based anesthetic. However, further studies are warranted to elucidate injury/protection mechanisms, optimal dose regimens, and investigation of more receptor selective narcotic selective.

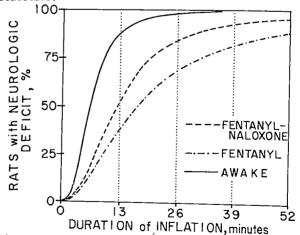


Figure 1-dose-response curves. There was a significant right shift in the fentanyl and fentanyl-naloxone dose response curves, with no significant difference between the fentanyl and fentanyl-naloxone curves (P< 0.05).

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Title: SUPERNATANT POTASSIUM LEVELS IN STCFFD BLOOD

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Introduction

Since the advent of blood component therapy, hyperkalemia following massive transfusion has been regarded as a rare occurrence. Miller and Brizca suggest that blood must be transfused in excess of 120 ml/min for clinically significant hyperkalemia to occur.(1) However, hyperkalemia has been reported at lower transfusion rates.(2) Adsol (Fenwal Laboratories) is a relatively new preservative mixture that is now routinely in use in the blood banks of this and other institutions. This combination of adenine, dextrose and mannitol permits the storage of packed red blood cells (PRBCs) at high hematocrits for as long as 42 days. Improved red blood cell survival is reportedly associated with less hemolysis and lower viscosity than that found in other PRBC storage preparations. Adsol purportedly "provides user convenience and avoids the potential risks associated with the dilution of concentrated red cells at the time of infusion."(3) Package enclosed product information includes measurements of supernatant potassium levels on day 35 and 42 of storage of 46 and 49 Meq/L respectively.(4) However, little information was readily available concerning the levels of supernatant potassium earlier than day 35. The current investigation was prompted by four children who received rapid transfusion of Adsol-preserved PRBCs. These four children exhibited clinical and laboratory evidence of hyperkalemia. This study reports changes in pH and the levels of supernatant potassium of Adsol-preserved PRBCs as a function of storage time.

Methods

Over approximately a three week period 100 units of Adsol-preserved PRBCs were randomly checked for supernatant potassium and pH immediately prior to transfusion. A 3 ml quantity of undiluted blood was withdrawn from each bag via a 21 gauge needle. This blood sample was immediately analyzed in the ABL4 Acid Base Laboratory by Radiometer and the age of the blood, pH, potassium and hemoglobin were recorded. The ABL4 was tested with known values of potassium containing solution to determine reproducibility in the range of 10 to 60 Meq/L. Calibration results showed the ABL4 to be accurate to + 0.19 Meq/L within this range. Supernatant potassium levels and pHs were plotted against the storage time of the blood. Simple linear regression was employed to obtain a formular description of the results for statistical analysis.

Results

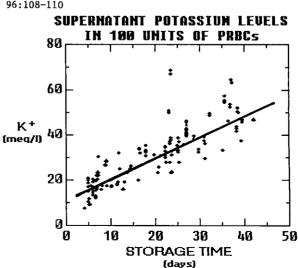
Linear analysis of the relationship between supernatant potassium and age of blood yielded a correlation coefficient of 0.88 and a standard error of estimate of 6.16. The relationship of pH to age of blood was also examined in this fashion and was characterized by a correlation coefficient of 0.85 and standard error of estimate of 0.11.

Discussion

Previous research on the Adsol type of PRBC storage has not sufficiently iterated the presence of supernatant potassium. This study showed that potentially dangerous levels of supernatant potassium rises linearly, as anticipated with age. However, units less than 10 days old contained unexpectedly high concentrations of supernatant potassium. In addition, most of the units had supernatant potassium levels greater than has previously been reported for CPD blood alone.(5,6) In summary, the decreased hemolysis reported as an advantage of Adsol blood does not result in a decreased supernatant potassium. Adsol blood, even when less than 10 days old, should be used with caution in young children, especially during rapid transfusion.

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TITLE: SUFENTANIL INFUSION: PHARMACOKINETICS COMPARED TO BOLUS

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 $\frac{Introduction.}{pharmacokinetics} \ \ Bovill, \ et \ al \ have \ described \ the pharmacokinetics of sufentanil after a single bolus of 5 <math>\mu g/kg$ in 10 surgical patients.\(^1\) More recent clinical practice, however, is to use a smaller dose of sufentanil as a bolus at the beginning of a case and to finish the anesthetic with either a volatile agent or a sufentanil infusion. The purpose of this study is to calculate the pharmacokinetics of sufentanil after a single dose of 1.5 $\mu g/kg$, to use the pharmacokinetic parameters to develop a reasonable protocol of sufentanil infusion, and finally to measure sufentanil levels in a group of patients

given the sufentanil infusion protocol.

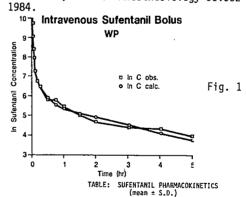
Methods. After this study was approved by the Human Subjects Committee, 18 patients scheduled for non- cardiac procedures involving general anesthesia were randomly selected from the operating schedule. After informed consent, patients were anesthetized with either the sufentanil bolus technique or infusion technique as follows: The Bolus Group (n = 12) was pre-oxygenated with 100% 0, for 2-3 min. Sufentanil 1.5 µg/kg was injected IV over thirty seconds. Thiopental was slowly infused until loss of lid reflex. Muscle relaxation was with vecuronium 0.1 mg/kg, with repeat doses of 0.015 mg/kg when necessary. After tracheal intubation, ventilation was controlled. Gas mixture was 70% $N_2{\rm O},~30\%~{\rm O}_2.$ Isoflurane 0.5 - 1.0% was administered to maintain the anesthesia. Reversal of muscle relaxant was with neostigmine 0.07 mg/kg and atropine 0.03 mg/kg IV. Extubation of the trachea occurred when patient responded to command. Blood samples for sufentanil were drawn prior to induction and at 1, 3, 5, 15, 30 min and 1, 2, 4, 6, 8, 12, and 16 hrs after induction. Sufentanil was analyzed by radioimmune assay, and the appropriate pharmacokinetic parameters were obtained in the same manner used by Bovill, et al. These parameters were used to develop the protocol for the Infusion Group. The Infusion Group (n = 6) was treated the same way with the following exceptions: Initial sufentanil bolus was 0.5 µg/min and the rate was then altered according to perceived anesthetic depth. Blood sufentanil levels were drawn at the same times as for the Bolus Group, except that a new "baseline" was drawn before the infusion was discontinued, and the sampling schedule was re-started, i.e., at 1, 3, 5, 15, 30, min; 1, 2, 4, 6, 8, 12, 16 hrs. The individual plasma concentration vs. time data were fitted to standard bi- and tri-exponential pharmacokinetic equations using a computerized least-squares method.

Results. The tri-exponential equation proved to be the best fit for the single-bolus sufentanil pharmacokinetics. The parameters derived are shown with the parameters derived by Bovill, et al in the Also, the calculated in sufentanil concentration as compared to the actual levels in one of the patients is shown in Fig. 1. There was no apparent correlation of volume of distribution with body weight (either total or estimated lean) or surface area. Total body clearance correlated with body surface area (r = 0.81), but less well with lean body weight (r = 0.62). The predicted sufentanil concentrations from the model, using an initial bolus of 0.5 $\mu g/kg$ and an infusion rate of

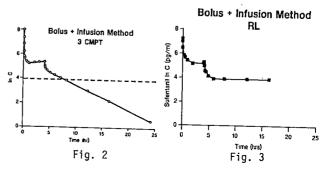
 $0.5 \mu g/kg/hr$ during a 4 hr procedure is shown in Fig. 2, where the dashed line represents the limit of detection of the assay (50 pg/ml). The actual data collected from a patient using this protocol is shown in Fig. 3.

Discussion. The limit of detection for this assay is about 50 pg/ml. For the 1.5 μ g/kg initial bolus, this was reached by six hours after induction. The intercepts (A,B,C) were less in our patients because the dose was less. Elimination the was longer, volume of distribution larger, and clearance faster in this group of patients than in the group studied by Bovill, et al, but these differences were not statistically significant. The infusion technique was designed to maintain a sufentanil level at 100-200 pg/ml. Unfortunately, the levels decayed so rapidly from this level at the end of the infusion that elimination kinetics could not be calculated from the after infusion samples. The infusion technique developed from the pharmacokinetic model of the bolus technique worked well clinically.

Reference Bovill JG, et al. Anesthesiology 61:502-506.



Pharmacokinetic Parameters	These Patients (n=12)	Bovill, et al ¹ (n=10)
A (pg/ml)	15,800 ± 7000	27,900 ± 11,384
B (pg/ml)	643 ± 266	5,900 ± 2,846
C (pg/ml	153 ± 57	1,040 ± 474
a (hr-1)	425 ± 7.9	37.8 ± 17.1
ß (hr-1)	2.17 ± 0.90	2.64 ± 1.14
y (hr-1)	0.17 ± 0.07	0.29 ± 0.09
tł (hr)	4.71 ± 2.16	2.73 ± 1.16
Vd (1/kg) C1 ⁸ (1/kg/hr) Vdss (1/kg) Vc (1/kg)	(1.8 - 10.6) 6.13 ± 2.52 0.93 ± 0.16 3.91 ± 1.89 0.107 ± 0.045	(1.6 - 5.7) 2.86 ± 0.80 0.76 ± 0.15 1.74 ± 0.6 0.164 ± 0.057



TITLE:

SUFENTANIL INFUSION: PHARMACODYNAMICS COMPARED TO BCLUS

AUTHORS:

R.C. Cork, M.D., Ph.D., J.A. Gallo, Jr., M.D., L.B. Weiss, M.D.,

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Introduction

Sufentan I has been compared with other narcotics for use in non-cardiac general anesthesia with clinical results at least as good and in some cases better than seen with the other narcotics. I The technique of administration has generally been to give a small bolus at the beginning of the case and to continue the anesthetic with either repeated bolus of the drug and/or the application of a volatile agent, e.g. isoflurane. The purpose of this study was to compare the clinical results of sufentanil bolus/isoflurane compared with sufentanil infusion.

Mathads

Methods After this study was approved by the Human Subjects Committee, 18 patients scheduled for non-cardiac procedures involving general anesthesia were randomly selected from the operating schedule. After informed consent, patients were anesthetized with either the sufentanil bolus technique or infusion technique as follows: The Bolus Group was pre-oxygenated with 100% 0, for 2-3 min. Sufentanil 1.5 µg/kg was injected IV over thirty seconds. Thiopental was slowly infused until loss of lid relfex. Muscle relaxation was with vecuronium 0.1 mg/kg, with reseat doses of 0.015 mg/kg when necessary. After tracheal intubation, ventilation was controlled. Gas mixture was 70% N₂O, 30% O₂. Isoflurane 0.5 - 1.0% was administered to maintain the anesthesia. Reversal of muscle relaxant was with neostigmine 0.07 mg/kg and atropine 0.03 mg/kg IV. Extubation of the trachea occurred when patient responded to command. The Infusion Group was treated the same way with the following exceptions: Initial sufentanil bolus was 0.5 μg/kg. Patients were then started on an infusion of 0.5 µg/min and the rate was then altered according to perceived anesthetic depth. Only 100 mg of thiopental was given, with an option to give an additional 50 mg if necessary for sedation. Neither group received pre-operative medication. Measured clinical variables included blood pressures, heart rates, wake-up time, presence of abnormal ECG, OR or RR complications, need for vasopressors, RR medication and recovery time. Also, electrolytes, renal and liver function were measured pre- and one day postoperatively. Results were analyzed using Student's t-tests for grouped and paired data and X analysis, with significance at p < 0.05.

Results

Of the 18 patients enrolled in the study, 12 were entered in the Bolus Group and 6 were entered in the Infusion Group. There was no difference between groups with regard to age, weight, sex distribution, ASA physical status, baseline chemistries and baseline blood pressures and heart rate. As expected, the Bolus Group used more

thiopental than the Infusion Group (227 ± 23 mg vs. 106 ± 15 mg, p < 0.001), and all the patients in the Bolus Group received isoflurane. There was no difference in amount of fluids administered or blood lcss between groups. Although there was no statistical differences in blood pressures or heart rate at any of the several observations made during the anesthetic, amount of change from baseline was statistically different at several points in each The Table presents the comparative heart rates during the procedures. A significant decrease in heart rate from baseline is seen for the Bolus Group at induction, after intubation, and after incision (p < 0.05), and a significant increase in heart rate in the Bolus Group is seen after extubtion and on recovery room admission (p < 0.05). No significant changes in heart rate were seen in the Infusion Group during the study. Pain medication was requested by 6 of 12 in the Bolus Group and 1 of 6 in the Infusion Group. Wake-up time and recovery time were not signficantly different between groups, and total sufentanil used was not significantly different between groups.

Discussion

The advantage of both these protocols over repeat boluses of sufentanil is that a bolus of sufentanil given near the end of a case may result in subsequent respiratory depression at the end of the case. Both the initial bolus technique with subsequent isoflurane and the sufentanil infusion technique avoid this risk. However, this study shows that the hemodynamic stability provided by sufentanil at the beginning of a case can be carried through to the end of the case with a sufentanil infusion, rather than by relying on isoflurane to finish the anesthetic.

Reference

 Flacke JW, Kripke BK, Bloor BC, Flack WE, Katz RL. Anesth Analg 62:259, 1983.

TABLE: HEART RATES DURING ANESTHESIA

Baseline $79 \pm 2_{\star}$ 78 ± 7 Induction $72 \pm 3_{\star}$ 74 ± 5 After Intubation $70 \pm 3_{\star}$ 80 ± 9 After Incision 63 ± 3 69 ± 4 At Reversal 86 ± 7 77 ± 8 At Last Skin Stitch $87 \pm 5_{\star}$ 84 ± 8 After Extubation $95 \pm 8_{\star}$ 86 ± 7		Bolus Group	Infusion Group
On RR Admission 97 ± 4 84 ± 7 At RR Discharge 81 ± 5 79 ± 4	Induction After Intubation After Incision At Reversal At Last Skin Stitch After Extubation On RR Admission	72 ± 3* 70 ± 3* 63 ± 3 86 ± 7 87 ± 5* 95 ± 8* 97 ± 4	74 ± 5 80 ± 9 69 ± 4 77 ± 8 84 ± 8 86 ± 7 84 ± 7

p < 0.05 from Baseline

TITLE:

THE SYSTEMIC AND PULMONARY VASCULAR EFFECTS OF CALCIUM IN THE POST-OP LOW CARDIAC OUTPUT STATE

AUTHORS:

R.C. Cork, M.D., Ph.D., Joseph A. Gallo, Jr., M.D., R. Smith, MSEE, CEE, and J. Copeland, M.D.

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Introduction

Although once widely utilized in patients with cardiac disease, use of calcium chloride or calcium gluconate is less common than in the past due to the debate concerning the effect of calcium on the myocardium versus the vasculature. 1 2 Modifying variables which can alter this effect, such as ionized calcium concentration, make the cardiovascu-lar actions of calcium even less predictable.The purpose of this study was to determine the systemic and pulmonary vascular effects of calcium chloride, in the absence of the natural myocardium, by utilizing the Jarvik-7 (TM), Total Artificial Heart (TAH).

Methods

Following approval by the institutional animal resources committee, five Holstein calves weighing 70-90 kg were studied. Under halothane anesthesia, a 7 Fr introducer was placed in the right external jugular vein along with an 18 gauge right femoral arterial catheter. The animals were allowed to recover from the anesthesia and were extubated. Six hours post-extubation a pulmonary artery catheter was placed and baseline measurements were obtained. Calcium chloride was then administered as a bolus through the sheath introducer at a dose of 4 mg/kg. Hemodynamic measurements were then repeated 1, 3, 5, and 10 minutes after the drug. Measurements obtained included heart rate (HR), systemic blood pressure (SBP), mean arterial pressure (MAP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Systemic (SVR) and pulmonary vascular resistance (PVR) and stroke volume (SV) were calculated from the above data. The following day the calves underwent placement of

On post-operative day 2, following collection of baseline measurements, a protocol identical to the above was implemented with the exception that left atrial pressure (LAP) was measured rather than PCWP. Cardiac output was determined by the Cardiac Output Monitoring Diagnostic Unit (COMDU) which monitors the performance of the TAH.³ The operational drive parameters and HR of the TAH were held constant throughtout the period of study.

Statistical analysis of the data was performed with a two-way ANOVA and Student's t-test for unpaired and paired data. Significance was set at p < 0.05.

The results are shown in Table 1 (Pre- and Post TAH). The results reveal that there are significant elevations in systemic systolic and diastolic pressure and pulmonary artery systolic pressure from baseline 10 minutes following bolus injection of the drug. No other significant changes occurred in the preopertive group. No significant changes occurred in any of the hemodynamic variables measured in response to calcium administration following implantation of the TAH.

Discussion

Calcium chloride is commonly utilized at the end of cardiopulmonary bypass (CPB) in an effort to counteract the effects of cardioplegia and dilutional hypocalcemia, thereby producing an improvement in myocaridal performance. Doses of 2-10 mg/kg have been shown to transiently improve myocardial contractility. The findings of this study illustrate that in the intact, preop animal, a clinical dose of calcium chloride has minimal cardiovascular effects. Further, this dose of calcium is devoid of significant effects on the vasculature in the animals who have undergone TAH implantation.

The findings of this study and others suggest that the clinical indications for the use of calcium may need to be redefined. In doing so, the use of calcium chloride in the clinical arena may be largely replaced by other inotropic agents that are both more potent and effective.

References

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TABLE 1
Percent Change From Baseline in Hemodynamic
Variable Pre- and Post-TAH (Mean ± S.E.)

		1 min	<u>3 min</u>	5 min	<u>10 min</u>
HR (beats/min) Systolic (mmHg) Diastolic BP (mmHg) PAP (systolic-mmHg) CO (liters/min) SVR (dynes-sec cm ⁻⁵) PVR (dynes-sec cm ⁻⁵)	Pre Post Pre Post	-2.6±3.5 0.2±2.2 5.0±2.9 -1.2±4.4 -13.0±16.1	-0.7±3.0 0±0.0 0.8±2.4 1.9±2.1 7.4±6.2 -10.1±10.4 12.6±3.9 -0.5±0.5 4.4±5.3 0.3±2.3 -3.6±5.8 1.8±4.0 -23.4±18.4 -15.9±10.8	1.5±1.6 0±0.0 1.4±1.6 1.9±1.2 12.0±5.7 -9.1±-10.6 7.6±4.6 0±0.0 4.4±5.1 -2.1±2.0 -0.03±7.9 5.7±3.6 -23.4±20.7 -8.5±7.6	3.0±2.6 0±0.0 10.9±6.8* 3.0±1.4 29.1±10.6* 20.5±7.6* 0±0.0 -0.2±4.7 0.7±3.0 16.9±12.8 3.1±4.0 1.8±8.4 -9.8±7.6

^{*} significantly different from baseline p < 0.05 x significantly different from post-artificial heart group p < 0.05

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MONITORING SEIZURE DURATION IN PATIE ITS UNDERGOING ELECTROCONVULSIVE THERAPY (ECT) Title:

LJ Couture, B.A., DR Thomas, B.S., SL Lippmann M.D., 1 HL Edmonds Jr., Ph.D. and LL Lucas, M.D. Authors:

Affiliation: Departments of Anesthesiology and ¹Prychiatry, School of Medicine, University of Louisville, Louisville, KY 40292

Introduction. The effectiveness of ECT for the treatment of endogenous depression is generally accepted to be related to both duration and generalization of the elicited seizure (1). Agents used in the anesthetic management of patients undergoing ECT are known to influence both (2), as well as make their assessment difficult. It is therefore important to anesthesiologists and psychiatrists alike that a simple and reliable method be available to assess the duration and generalization of seizure activity. The purpose of this study was to examine the interrelationships among four common methods presently used to measure duration of seizure activity.

Methods. We examined the intraoperative records from 14 consecutive ECT treatments of 3 patients. Anesthetic management of these patients included the following: 0.005 mg/kg glycopyrrolate pre-op, 1.2-1.5 mg/kg methohexital for induction, and 1-2 mg/kg succinylcholine to produce neuromuscular blockade. Routine monitoring included ECG, blood pressure, and inspiratory O2 and end-tidal CO2. Neuromuscular blockade was measured by the electrically evoked muscle potential (EEMP) from the abductor pollicis. Monitoring of seizure activity was independently assessed by the cuff method (3), unprocessed EEG, mean integrated EEG amplitude (MIA) and forehead electromyogram (FEMG). The latter two were obtained from the DATEX/Puritan-Bennett Anesthesia and Brain activity Monitor (ABM). The FEMG and MIA were determined by selective filtering of biopotentials obtained from surface electrodes placed over the temporal bone (ground), on the mid-forehead (active), and over the mastoid process (reference). The FEMG measurement range was 0-15 μV rms at 70-300 Hz. MIA ranged from 0-100 μV rms at 1.5-25 Hz. Both FEMG and MIA were displayed on a video monitor and graphic hardcopy in successive 10-second epochs. The digitized values of the FEMG and MIA were stored to floppy lisc for later statistical comparison. An increase in FEMG and MIA of greater than 50% of the pre-ECT paseline was considered as evidence of seizure activity.

Results. The mean and s.d. in seconds for the luration of seizure activity as assessed by each of the methods was found to be as follows: cuff 7+14, FEMG 62+14, MIA 79+30 and EEG 84+31. A Milcoxon signed rank test revealed no significant lifference between any of the measures of seizure luration. Table 1 shows the Pearson Product-Moment 'orrelation Coefficients and the significance evels obtained. All methods for determining the luration of seizure activity were significantly correlated.

Discussion. The mean duration of cortical seizure activity may be slightly underestimated by the MIA. This may be due to the signal processing technique. The FEMG seems to provide a more sensitive, as well as more objective, measure of motor seizure duration. The cuff method depends on the subjective evaluation of an observer. Increases in FEMG activity persisted despite an absence of visible motor movement. Such an objectively sensitive measure of motor activity may be useful in future evaluations of the effect of various anesthetics on motor seizure duration. Figure 1 shows a typical response obtained in a single patient. Note that the FEMG remains responsive despite the profound neuromuscular blockade.

Acknowledgments. The authors wish to thank the Puritan-Bennett Corp. for providing the ABM used in this study.

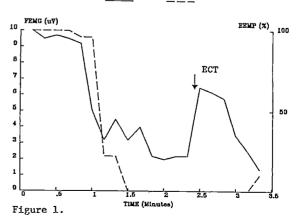
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Table 1. Correlation matrix

	CUFF	MIA	EEG
FEMG	0.72*	0.65*	0.62*
CUFF		0.79**	0.76*
MIA			0.98**
*p=<0.0	1 **p=<0.00	01	0.50

FEMG DURING ELECTROCONVULSIVE THERAPY FEMG EEMP



EUPIVACAINE (B) AND LIDOCAINE (L) FUNCTIONAL AND METABOLIC INFLUENCE IN ISOLATED WORKING RAT HEART Title:

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Introduction. The relative cardiac depressant effects of (B) compared to (L) have been reported to range from approximately 4:1 in vivo in pigs (1) to 36:1 in isolated guinea pig atria (2). Using the more physiologic working rat heart, we have examined the comparative cardiac toxicity and effect on glycolysis and energy metabolism of (B) and (L).

Methods. Ad libitum fed male Wistar rats, 250-275 g, were anticoagulated with 1000 units of heparin administered intraperitoneally and anesthetized with i.p. pentobarbital, 30 mg. hearts were removed, mounted as a Langendorff preparation and perfused with 60 ccm H2O pressure of Krebs Hensleit solution containing 10 mM glucose with or without insulin, 10 units/L. After approximately 10 minute washout and stabilization, they were converted to a working preparation with 10 cm H2O left atrial filling pressure. Following an additional 15 minute stabilization period, a 15 minute experimental period was begun; the perfusion fluid could then be changed by means of a 3-way stopcock to introduce perfusion fluid containing 2-3H-glucose with or without local anesthetic (LA). (B) was added in concentrations of 2.5, 5.0, 10.0, and 12.5 mg/L and (L) 10, 25, 40, and 50 mg/L. in coronary effluent was measured to estimate glucose uptake. Lactate production and tissue glycogen were measured by enzymatic methods. Nucleotides and creatine phosphate were measured with HPLC. Coronary effluent was collected at 13-15 minutes from the pulmonary artery and mechanical events recorded at 15 minutes. The hearts, when desired, were freeze clamped at 15 minutes. Statistical procedures were performed on the regression of the LA dose versus effect using commercially available software.

Results. Both LA's produced a dose-dependent decrease in heart rate (HR), cardiac output (CO), coronary flow (CoF) and myocardial O2 consumption (MVO₂). Insulin did not influence these effects. $\overline{\text{Table}}$ 1 shows these regression plots. The relative depressant potencies may be expressed as a ratio of their slopes, SB/SL, and are tabulated. B and L both decreased glucose uptake (GU) and lactate production in a dose-related manner. The effect on GU was greater during insulin infusion. Neither LA affected tissue glycogen nor high energy phosphates (HEP). When the B concentration was "normalized" by multiplying by 4.59, the effect of the LA's on glycolysis were statistically similar.

Discussion. In the working rat heart, after 15 min of perfusion, B had a depressant effect of approximately 4.5 times that of L. In isolated guinea pig atria, the B/L ratio on spontaneous heart rate depression was approximately the same as our results but contractile depression was considerably greater (2). In isolated guinea pig trabeculae, stimulated at 3Hz, the relative potencies of 10 mM B and 40 mM L were nearly equal (3). At slower

frequencies B was much more potent, however. In studies on Langendorff heart preparations in rabbits (4) and guinea pigs (5), the negative inotropic effect of B was more than 10 times that of L. But the Langendorff preparation is not as physiologic as the working heart. In addition, only with prolonged perfusions were these high ratios seen in one prep (5) which suggests that the effects were either related to an intracellular locus or perhaps to the prolonged effect of B vs L (6). It is also of interest that the LA's had more effect on GU in the insulin stimulated hearts. Both LA and insulin stimulation of GU effects are mediated through the cell membrane. In summary, in the working rat heart, the effect of B and L on function was equivalent to their LA potency as was their effect on glycolysis and MVO2. The lack of effect of either B or L on HEP suggests that the cardiac effects are not mediated through energy metabolism.

Table 1. B and L influence on cardiac function and oxygen consumption.

Parameter	<u>LA</u>	Intercept	Slope	SB/SL
HR	В	245.45	-13.90	5.49
	L	245.70	- 2.53	
MP	В	82.27	- 3.05	4.07
	L	82.54	- 0.75	
CO	В	53.14	- 2.11	4.91
	L	53.32	- 0.43	
CoF	В	14.96	- 0.74	4.35
	L	15.62	- 0.17	
MVO ₂	В	7.66	- 0.37	4.11
-	L	7.76	- 0.37	

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Anesthesiology 1985; 62:396-405

TITLE:

CARDIOVASCULAR CHANGES AFTER MIDAZOLAM IN PATIENTS WITH AORTIC STENOSIS: EFFECT OF NITROUS OXIDE

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INTRODUCTION: The hemodynamic effects of the common combination of midazolam and nitrous oxide have not previously been studied in patients with aortic stenosis. Since this is a relatively high risk group of patients during anesthesia induction, and since midazolam and N20 may be used for anesthetic induction in these patients, we examined the hemodynamic effects of this anesthesia

combination. METHODS: With institutional review board approval 16 patients scheduled for aortic valve replacement were studied. Patients had severe aortic stenosis. The patients were premedicated with diazepam .1 mg/kg, morphine sulfate .1 mg/kg and scopolamine 0.2 mg one hour prior to study. Catheters were placed in a peripheral vein for drug and fluid administration, in the radial and pulmonary arteries for continuous pressure measurements. Leads I, II and V_5 were monitored for evidence of ischemia or rhythm changes. lfter basline measurements, .2 mg/kg midazolam IV vas given in 5 sec. Eight patients received 100% % mygen, nine patients received 50% N20 and 50% N2. No muscle relaxants were given. Ventilation vas assisted, if necessary. Hemodynamic variables were recorded at one, three and five minutes after induction, since previous studies have shown that peak hemodynamic changes occur by hese times. Hemodynamic variables at each stage of measurement were tested for group differences using a repeated measure analysis of variance. A -value <0.05 was declared significant. ESULTS: The patient characteristics are listed n table 1. The peak aortic gradient was 83 mmHg n the $N_2\text{O}$ group and 75 mmHg in oxygen group. ll patients were anesthetized in less than 30 econd. Midazolam significantly reduced the mean rterial blood pressure (MAP) in both groups of atients at 1 and 3 minutes the oxygen group was lso reduced at five minutes (table 2). The ecrease in MAP did not precipitate any myocarial ischemia or rhythm disturbance. The heart ate (HR) was significantly reduced in the oxygen roup at 3 minutes. Cardiac index (CI) signifiantly fell at 5 minutes in the oxygen group. he pulmonary diastolic pressure was reduced ignificantly in the oxygen group at 3 min. and he nitrous group at 5 min. SVR significantly ecreased from baseline only in the nitrous oxide

ISCUSSION: Overall hemodynamic changes after idazolam were relatively minor, primarily a ecrease in blood pressure. The decrease in BP

tended to be a result of decreased CI in the oxygen group and SVR in the N_2 O patients. This is similar to the hemodynamic effect of midazolam in patients with ischemic heart disease 1 . The addition of N20, well known to depress cardiac function in conjunction will opioids, has negligible affects with midazolam. We conclude that midazolam can be used safely for induction with or without N_2O in patients with severe aortic stenosis.

TABLE 1. Patient Characteristics. Mean + S.D.

Wght(kg) BSA(m2) AGE(yr) RAP(mmHg) MAP(mmHg) PAD(mmHg) EF(%) CI(1/min/m2)	N ₂ 0 n=9 70.7+15.9 1.80+.25 61+11 5+3 96+17 16+6 55+12	0 ₂ n=8 76.5+16.4 1.78+.20 65+12 4+3 102+22 17+8 55+13
CI(1/min/m2) Valve Gradient(mmHg)	2.71 <u>+</u> .59 82.5 <u>+</u> 31.5	55 <u>+</u> 13 2.91 <u>+</u> .70 75.8 + 43.8

TABLE 2. Hemodynamics. Mean + S.D.

				-		
Baseli	HR De	RAP	MAP	PAD	CI	SVR
N ₂ 0 0 ₂	69±13 68 <u>-</u> 6	9 <u>+</u> 5 8 <u>+</u> 6	84 <u>+</u> 10 84 <u>+</u> 21	19 <u>+</u> 8 19 <u>+</u> 11	2.5 <u>+</u> .4 3.0 <u>+</u> .7	1326 <u>+</u> 337 1189 <u>+</u> 332
+1 Min N ₂ O O ₂	• 69 <u>+</u> 6 67 <u>+</u> 6	10 <u>+6</u> 8 <u>+</u> 7	77 <u>+</u> 10* 74 <u>+</u> 15*	17 <u>+6</u> 18 <u>+</u> 13		1326 <u>+3</u> 93 1107 <u>+</u> 298
+3 Min N ₂ O O ₂	66 <u>+</u> 6 64 <u>+</u> 6	10 <u>+</u> 5 7 <u>+</u> 5	71 <u>+</u> 10* 66 <u>+</u> 16*	24 <u>+</u> 18 16 <u>+</u> 10*	2.4+.3 2.6+.5	1117 <u>+</u> 301* 1077 <u>+</u> 298
+5 Min						
N ₂ 0 n=3	64 <u>+</u> 9	6 <u>+</u> 2	70 <u>+</u> 12	13 <u>+</u> 4*	2.5 <u>+</u> .3	1209 <u>+</u> 460*
0 ₂ n=5	<i>63</i> <u>+</u> 10	8 <u>+4</u>	66 <u>+</u> 20*	15 <u>+</u> 6	2.4 <u>+</u> .5*	1116 <u>+</u> 433
*n<0.0	5 from	haselin	פר			

^{*}p<0.05 from baseline

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⁺p<0.05 between groups N_20 and O_2

SUFENTA REQUIREMENTS, PLASMA SUFENTA AND CATECHOLAMINE LEVELS AFTER DIAZEPAM

DURING CABG SURGERY

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Introduction: Fentanyl requirements to induce unconsciousness (U) after pre- treatment with diazepam (D_z) are well documented (1). That information is lacking for sufentanil (Sf). We examined therefore the Sf requirements to induce U and the subsequent hemodynamic (H) response and plasma (Pl) Sf, and catecholamine (CAT) levels following orotracheal intubation (TI), skin incision (Sk), sternotomy (St) and before cannulation of the great vessels (APB) in patients scheduled for CABG pretreated or not with Dz.

Fourteen patients with CAD scheduled for CABG surgery, were studied after informed consent. Age ranged from 45 to 72 years, and body weight from 62 to 90 kg. Seconal 1.5 mg/kg and morphine sulfate 0.1 mg/kg were given IM, I hour prior to surgery. Preparation included a 5-lead EKG, the infusion of lactated Ringers and radial artery cannulation for BP monitoring. After random assignment to the combination Dz-Sf (DS, n=7) or Sf alone (S, n=7) and 20 mcg/kg of pancuronium (P) IV, DS treatment was started with 100 mcg/kg of Dz followed by a Sf infusion of 150 mcg/min. Ventilation (V) was assisted with 100% 02. Patients were asked every 15 sec. to open eyes and to take a deep breath. Failure to comply with three consecutive commands was defined as U. Then, 80 mcg/kg of P were injected and V controlled, followed 3 min. later by TI and mechanical V with 100% 02. After right atrial cannulation through the IJV, 150 mcg/kg of Dz were injected followed by the same dose of Sf that caused U. With the omission of Dz, the same protocol was used with S. Heart rate (HR), systolic and dastolic blood pressure (SBP and DBP) were recorded before induction of anesthesia [baseline(B)], before and after TI, Sk, and St and at Blood samples for the measurement of Sf levels by RIA (Janssen), Pl CATs by LCEC, and Dz levels by GC were taken at B, 2 min after TI, Sk and St and at ABP. The rate-pressure product (RPP) was computed as the product of HR and SBP and used as an index of cardiac work (CW). If SBP rose 15% above control values and/or DBP above 90 mm Hg for more than 1 min, up to 3 boluses of 50 mcg of Sf were injected at 1-min. intervals. If SBP and/or DBP did not return to the normal range with this treatment, enflurane and nitroglycerin were added. One- and two-way analysis variance(ANOVA-I-R, -2-R) Newman-Keuls and unpaired t-tests were used for statistical analysis.

Results: H values, plasma Sf, Dz, and CAT levels and standard deviations () are listed in the table. Statistically significant differences (SSD) between the groups at B were not observed. Average Sf doses to induce U were 147.3 (47.4) mcg or 2.31(5.6) mcg/kg with DS and 356.3(114.1) mcg or 4.6(1.7) mcg/kg with S (p<0.01). With DS, ANOVA-1-R

revealed SSDs in the overall changes of RPP (p<0.05) and of SBP, Pl epinephrine (E), norepinephrine (NE), E + NE , (p<0.01). SSDs from B for the individual variables are marked in the table as a (p<0.05) and b (p<0.01). With S, SSDs only for NE (p<0.05) were observed. ANOVA-2-R showed that DS significantly influenced the overall changes in SBP and RPP (p<0.01), Pl E, NE + E and Sf (p<0.05) compared to S. Specific SSDs between S and DS are marked in the table with d (p<0.05) and b (p<0.01).

Discussion: Compared to S, DS treatment halved the Sf dose to induce U, decreased further requirements and plasma levels of Sf, decreased the pressure component of afterload, RPP and Pl CATs at various events. The Sf doses that produced U with S confirm data of other studies⁽²⁾. However, in the absence of Dz, Sf did not prevent BP to increase after TI and failed to decrease RPP and Pl CATs.

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We acknowledge the support of Janssen Pharmaceutica.

			TAE	ŗřÉ		
			Bve	nte		
		В	TI	Sk	St	APB
HR (b/min)	S	69(10)	75(9)	71(10)	74(8)	70(9)
	DS	70(8)	65(10)	65(11)	69(11)	71(10)
SBP (== Hg)	s	142(9) 152(35)	155(21)° 115(28)b	140(10)° 121(12)°	151(17) 133(21)=	134(7)4 123(9)=
DBP (mm Hg)	S	74(13)	81(12)	77(9)	81(9)	75(12)
	DS	77(16)	64(14)	71(15)	76(12)	78(9)
RPP	S	97(16)	123(35)ª	98(18) ⁴	112(21)	94(14)
(b.mmHg/min.102)	D5	107(31)	76(24)ª	78(15)•	91(16)	90(15)
Plasma E	S	20(14)	17(22)	12(15)	12(12)	16(12)4
(ng/100 ≡1)	DS	24(15)	8(11)b	6(4) ⁵	4(3)*	5(3)b
Plasma NE	S	36(22)	37(20)	30(11)	34(16)	53(26)
(ng/100 ml)	DS	45(24)	23(11)*	18(8)*	21(9)•	37(13)
Plusms E + NE	s	55(24)	53(28)	40(11)	46(19) ⁴	83(25)°
(ng/100 ml)	Ds	69(37)	31(15)b	24(10)	26(8) ⁶	42(13)°
Plasma Sf	S	19(19)	969(910)		1041(746)b.d	794(423)***
(ng/100 ml)	DS	20(16)	242(143)		158(39)a	138(72)*
Plasma Dz (mcg/100 ml)	DS	20(0)	35(9)*	93(32)	82(24)	43(21)•

Mean hemodynamic, plasma catecholamine, sufentanil and disrepam lovels and standard deviations () at baseline (8), after trachesi intubation (71), mkin incision (Sk), sternotosy (St) and before cardiopulmonary bypass (ABP) in patients treated with sufentanil alone (S, n=7) and disrepam-sufentanil (DS, n=7) and the standard of the st

(DS, n=7)
a and b: significantly different from baseline for p < 0.05 and < 0.01
respectively
d and D: significantly different from DS for p < 0.05 and 0.01 by unpaired
t test.

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Title: EFFECT OF VERAPAMIL ON HEMODYNAMICS AND

LEFT VENTRICULAR BLOOD FLOW IN A-ESTHETIZED DOGS.

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Introduction: Verapamil (V) is a calcium channeblocker with important cardiac and vasoactive properties. 1 Although V has been reported to be a coronary vascdilator, its effect on left ventricular blood flow (LVBF) in anesthetized subjects is least clear. 2 We investigated the effect of V CT hemodynamics and left ventricular blood flow (LVB3 in anesthetized dogs.

Ten mongrel dogs (17-25 kg) received 🛫 mg/kg IV of sodium pentothal and 2 mg/kg IV +1 succinylcholine, had tracheal intubation, maintenance of anesthesia with 0.9% end-tidal isoflurane in 5C? N_2O and O_2 , pancuronium (1mg/kg) and ventilation controlled to maintain PaCO2 between 35 and 40 tor-End-tidal CO₂ was monitored by infrared analys. = and temperature maintained beween 37 and 38. Heart rate(HR) was monitored from the ECG. A 7 3 pulmonary artery (PA) catheter, inserted through the right EJV, provided PA and pulmonary capillary wedge pressures (PCWP) and CO by thermodilution. The femoral arteries were cannulated retrogradely for (1) aortic pressure monitoring, (2) insertion of = pigtail catheter into the LV for the injection of 15 J microspheres, radioactively labeled with 141Ce, and 85Sr, for LVBF and 3) arterial blood ge measurements. Mean arterial and PA pressures (MAZ and MPAP) and systemic vascular resistance (SVE) were derived from standard formulae. After baselir= (B) measurements, V treatment (n=5) consisted of \equiv bolus of V (250 mcg/kg over 4 min) followed by a continuous infusion of 1 mcg/min. Five other animals received equivolumetric amounts of saline(S. All measurements were repeated 15 min after the start of the infusion of V or S. After sacrificing the animals, the heart was removed and an LV wall sample taken for gamma spectrometry by a Beckman gamma counter for LVBF measurement. Data wer= expressed in percent of baseline and analyzed for statistical significance using paired and unpaired 1

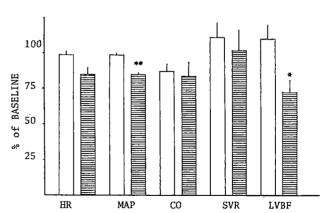
Results: At B, no statistically significant differences (SSDs) were found between the groups. After S, m SSDs from baseline were found. After V, systolic (SBP), diastolic (DBP) and MAP dropped by 13% (p = 0.02), 17% (p < 0.001) and 15% (p < 0.001 respectively and LVBF decreased by 29.6% (p < 0.02).No other SSDs in hemodynamics variables were found. Linear regressions between LVBF on the one hand and SBP and DBP on the other yielded correlation coefficients of 0.77 (p] 0.05) and 0.34 respectively. When comparing V to S SSDs were found for blood pressure and LVBF (sea figure).

Discussion: Isoflurane and V have hypotensive and coronary vasodilating effects. Here V caused not only a significant fall in blood pressure but also a fall in LVBF. The correlation coefficient of 0.77 found between the V-induced decrease in SBP and LVBF may indicate that V may have interefered with autoregulatory mechanisms of LVBF and made it more In conclusion, the acute pressure dependent. administration of V is anesthetized dogs caused mild hypotension and decrease in LVBF.

Partly supported by a grant of the AHA, chapter NE Ohio.

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Mean % of baseline and SEM of hemodynamic variables and LVBF after saline (open bars, n=5) and after verapamil (striped bars, n=5) in anesthetized dogs. Intergroup differences at p<0.02 (*) and p<0.01 (**) by unpaired t tests.

Title: PULSE OXIMETRY DURING THORACIC SURGERY: NOT THE "GOLD STANDARD" FOR OXYGENATION.

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<u>INTRODUCTION</u>: Pulse oximetry has become a monitoring standard in patients with pre-existing lung pathology undergoing thoracic surgery, where changing intrapulmonary shunting can result in hypoxemia. Brodsky et al reported a close correlation between the Nellcor N-100 and directly measured oxygen saturations (SaO $_2$) in these patients. Our experience does not agree and we feel this is of clinical importance particularly in patients undergoing thoracic operations.

METHODS: With the approval of our Investigational Review Board, twenty adult patients ASA II-III, mean ages = 56 years ± 3 SE were studied during thoracic operations in the lateral decubitus position. A radial artery cannula was inserted and pulse oximeter finger probe sensors for the Nellcor N-100 (Nellcor Inc., Hayward, CA) and the Novametrix Model 500 (Medical Systems Inc., Wallingford, CT) were placed on the same hand. Anesthesia was induced with thiopental and maintained with nitrous oxide 50% in oxyger, isoflurane, (.5-1.5%), sufentanil, and pancuronium iv as needed. Ventilation was controlled with a tidal volume of 10ml/kg at a rate of 8-10 breaths per minute. Arterial blood was sampled for PaO₂ and SaO₂ (Corning model 2500 Co-oximeter) at the following times: 1)immediately prior to induction, 2) immediately after induction, 3) during bronchoscopy, 4) after positioning, 5) after the chest was opened, 6) at 15 minute intervals thereafter until the end of the procedure, and 7) when the patient was again supine. The blood SaO₂ values were compared to simultaneous readings recorded from the digital displays of the two pulse oximeters. Data were subjected to analysis of variance. P<.05 was regarded as significant.

RESULTS: A total of 255 matched observations were recorded. The most common 0, saturation from the Nellcor was 100%, compared to 98% for the Novametrix and 96% from the Co-oximeter (Fig 1). The Nellcor readings were statistically different from the Co-oximeter at the P<.001 level while the Novametrix were statistically different at the P<.05 level. To eliminate variables such as changes in temperature, pH, and anesthetic effects, we focused on values obtained prior to anesthesia while patients were breathing room air (Fig 2). The simultaneous values recorded from the Nellcor, Novametrix, and Co-oximeter are compared with the normal Hgb-0, dissociation curve. Both the Nellcor and the Novametrix overestimated the SaO₂, while the Co-oximeter closely approximated the normal curve. Even at these lower SaO₂ levels, the Nellcor values were statistically higher than those determined by either the Co-oximeter or the Novametrix (P<0.05).

DISCUSSION: Our clinical experience with pulse oximetry agrees with others' in that it is a valuable modality for following trends in SaO, during thoracic surgical procedures, particularly when rapid fluctuations occur due to anesthetic or surgical manipulations. The data presented here, however, indicate that pulse oximetry, and particularly the Nellcor, is inadequate for estimating arterial

oxygen tension at the "knee" of the oxyhemoglobin dissociation curve. For example, a SaO₂ value of 99-100% obtained with a Nellcor device could lead to the conclusion that the patient's PaO₂ was in excess of 150 mmHg, whereas the corresponding mean PaO₂ in figure 2 is only 91 mmHg. It is only when the SaO₂ was as low as 94% for the Nellcor and 97% for the Novametrix that the expected PaO₂'s corresponded to the actual blood gas tension measurements. We conclude, then, that while pulse oximetry is valuable for following trends in perioperative oxygenation, it does not replace direct measurement of PaO₂ for accurately evaluating a patient's ability to oxygenate at any given point during a thoracic surgical procedure.

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 $\begin{array}{ccc} & FIGURE & 1 \\ & \text{DISTRIBUTION OF 0}_2 & \text{SATURATION MEASUREMENTS} \end{array}$

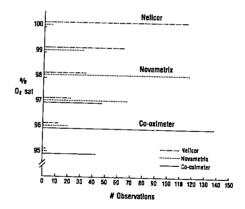
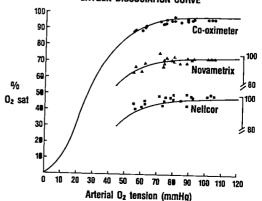


FIGURE 2 Oxygen dissociation curve



Title: CARDICVASCULAR EFFECTS OF PANCURONIUM, VECURONIUM AND ATRACURIUM DURING INDUCTION OF ANESTHESIA WITH SUFENIANIL FOR CABG

AUTHORS: MS, Dhamee, M.B.B.S, AC, Reynolds, M.D., J. Entress, M.D., T. Olund, M.D., J. Kalbfleisch, Ph.D.

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The combination of muscle relaxant and narcotic utilized to anesthetize patients with coronary artery disease should not produce hemodynamic instability at the time of induction of anesthesia.

This study was done to compare the hemodynamic effects of pancuronium(P), vecuronium(V) and atracurium(A) during induction of anesthesia with sufentanil in patients undergoing elective CABG.

METHODS

Thirty one patients who were scheduled for elective CABG were studied in a double blind protocol. The study was approved by the human research review committee. Beta blockers, calcium channel blockers and other medications were continued until the morning of surgery. Patients were premedicated with morphine sulphate 0.15 mg/kg and Scopolamine 0.3 mg to 0.6 mg intramuscularly 1-1 1/2 hours before induction of anesthesia.

Induction of anesthesia was standardized to sufentanil 8ug/kg diluted to 100 ml of normal saline and infused over 8-10 minutes. 4 mg of lorazepam was given during the infusion. Pancuronium 0.1 mg/kg or vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg were infused simultaneously.

Hemodynamic measurements were recorded at the following times: <u>Period 1</u>: In operating room before induction of anesthesia. <u>Period 2</u>: Two minutes after completion of sufentanil and muscle relaxant (MR). <u>Period 3</u>: Five minutes after completion of sufentanil and MR. <u>Period 4</u>: Immediately after intubation.

Differences in patterns of mean responses between the three study groups were analyzed by analysis of variance (repeated measures) and the least significant difference test (LSD). Probability levels of 0.05 or smaller are used to indicate statistical significance.

RESULTS

The hemodynamics during the study periods are presented in Table 1. The change in the mean HR from Period 1 to Period 3 differs between the three drug groups. Pancuronium increases mean HR, while atracurium and vecuronium produced mean heart rate decline. The heart rate changes when compared as vecuronium vs

pancuronium and atracurium vs pancuronium showed a statistical significance of P(005. Atracurium vs vecuronium was of no statistical significance.

No significant inter-group differences were seen in MAP, PCWP, CO, CI, SI, SVR, PVR, LVSWI AND RVSWI.

DISCUSSION

Our study shows that there are no differences in hemodynamic changes between P, V and A when used with sufentanil except the heart rate which increases with P. There are no differences in any of the parameters between Y and A, therefore, they have no advantages over one another as the muscle relaxants of choice for CABG.

	PERICD 1	PERIOD 2	PERIOD 3	PERIOD 4
HR				
P V A	68.3±15.0 72.4±15.4 79.1±18.9	71.1±12.1 66.6±12.5 69.0±13.4	70.9±14.2 63.6±13.2 68.3±14.2	74.3±13.0 65.8±11.1 74.2±13.5
MAF	<u>></u>			
P V A	100.5±16.2 94.3±13.1 94.0±18.9	83.1±13.4 73.1±15.1 64.8±8.5	83.2±13.6 75.8±13.1 69.9±11.5	89.4±13.3 81.1±14.0 74.7±14.6
PCV	<u> P</u>			
P V A	16.0±5.29 17.3±8.37 18.56±6.98	13.55±4.74 14.63±4.90 14.78±6.51		14.73±5.61 14.23±5.37 15.56±6.11
<u>CI</u>				
P V A	2.91±0.81 3.05±0.89 3.01±0.56	2.77±0.88 1	.64±0.77 2	.86±0.57 .70±0.58 .66±0.19

HEMODYNAMICS OF HEART TRANSPLANT RECIPIENTS IMMEDIATELY FOLLOWING CARDIOPULMONARY BYPASS

Authors:

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Introduction. The early physiology (1st week) of heart homografts (HH) has been previously reported 1. However, there is no data during the first 24 hours postoperatively. The purpose of this study was to measure hemodynamic determinants of ventricular performance of HH early after cardiopulmonary bypass (CBP).

Methods. 15 HH recipients (NYHA III-IV) (71+15 kg, 54+13 yrs, 1.8+.2 m² BSA) were premedicated with kg, $\overline{54+13}$ yrs, 1.8+.2 m² BSA) were premedicated with lorazepam (10-30 mcg/kg), induced with fentanyl (15 + 12 mcg/kg) cr ketamine (1.2+.6 mg/kg) and succinylcholine (1.9+.7 mg/kg), sterilely intubated, paralyzed with vecuronium (.1 +.07 mg/kg), and isoflurane (.25-.75%, 0_2 and air, $Fi0_2 > .7$) while mechanically ventilated ($PaCo_2 < 33$ mmHg, PEEP = 5 cm H_2O). Hypothermic (28°C, Plasmalyte° prime) CPB, (Hct 25%, Q = 1.8 L/min/m² BSA, MAP = 70 mmHg) was used with isoflurane (.25-1%) vaporized in the oxygenator (control MAP, amnesia). Arrested HH (cold K⁺ cardioplegia), preserved in iced saline oxygenator (control MAP, amnesia). Arrested HH (cold K⁺ cardioplegia), preserved in iced saline were grafted by standard techniques². With mechanical ventilation restored, (FiO₂ = 1.0, isoflurane .25-.5% inspired, PEEP = 5 cm H₂O, PaCo₂ < 33 mmHg) CaC⁺ and pH corrected, CPB was discontinued (CVP < < 15 mmHg, CI > 2.5, HR > 100 bpm). Isuprel (ISU), dobutamine (DBT), dopamine (DOP), nipride (NTP), nitroglycerine (NTG) were used (mcg/kg/min) to maintain CI > 2.5 L/min/m² before and after CPB. Ischemia (TT), reperfusion (RT), and CPB time (CPBT) were noted. Hemodynamic profiles were obtained at 20, 40, and 60 minutes and then at 3-4 hours after CPB for 24 hr. Heart rate (HR, bpm), mean aortic pressure (MAP, mmHg) central venous pressure (MAP, mmHg) central venous pressure (CVP,mmHg), mean pulmonary artery pressure (MPAP, mmHg), pulmonary artery diastolic pressure (PADP, mmHg), cardiac index (CI, L/min/m² BSA), stroke volume index (SVI, mL/min/m²), total pulmonary and (TDVRI) systemic vascular resistance indices (TPVRI and SVRI, SVRI, dynes sec cm $^{-5}$ m 2) were measured or calculated (standard equations 3); blood gases, Hct, FiO₂, P_{AO₂} (A-a)O₂ and drug support were recorded during measurements in ventilated patients under Analysis of variance for sequential comsedation. parisons (EPISTAT®) was used to determine significance.

Results. 15 HH (IT 163 \pm 65 and RT 51 \pm 17 min) were transplanted. Hemodynamics (Fig 1) and drug support (Fig 2) 20 min off CPB were: HR 109 + 12, MAP 71 + 9, MPAP 25 + 5, PADP 18 + 5, CVP 15 + 5, CI 4.3 + 1.4, SVI 40 + 16, SVRI 1130 + 304, TPVRI 507 + 219, ISUP (.01-.02, 5 of 15), DBT (6 + 3, 13 of 15) DOP (1 + 2, 5 of 15), NTG (3 + 1, 14 of 15) and NTP (3 + 2, 14 of 15). Within 3-6 hs there were trends to a decline in HR, CVP, PADP and TPVRI with a rise in SVRI (Fig 1). Transient increases in SVRI and TPVRI cause falls in SVI and CI (Fig 1). SVI was well maintained at its 20 min value (Fig 3). Inotropic requirements decreased (3-6 hr), while vasodilators were needed for 24 hr (Fig 2).

Discussion. Transplanted HH have adequate first 24 hr performance if maintained with inotropic and vasodilator support. The observed trends suggest an early improvement in ventricular compliance and a known $^{\! 1}$ more permanent dependance on HR and loading conditions. Early systolic performance (SVI) was better than previously reported at 24 hr because of aggressive control of loading conditions with vasodilator therapy.

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Figure 1 OR ICU 1400 600 • SVRI □ TPVRI 1000 300 50 115 • SVI D HR 30 95 90 26 MAP O MPA 70 20 20 17 O CVP PAD 15 9 5.0 3.5 Figure 2 5 NTP □ NTG Ż 2 1.0 8 .03 ● DOP DOB AISU 3 0 20 40 60 11-14 23-26 Minutes Hours

*Significantly different (p<.05) from mean of 60 minute sample

PREBYPASS CHANGES IN PULMONARY VASCULER IMPEDANCE DURING HEART TRANSPLANTATION

Authors:

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Affiliation: Department of Anesthesiology, Univer∈ity of Minnesota Health Sciences Center, Minneaapolis, MN

Introduction. Transient right ventricular dysfunction (RVD) after bypass is common among hear-recipients who fulfilled pulmonary vascular imperiors. dance (PVI) criteria for transplantation (1), Intraoperative factors may increase PVI, a known determinant of RVD. This study examines the effects of anesthesia and supportive interventions on total pulmonary vascular resistance index (TPVRI), a measurement of PVI, before CPB.

Methods. Heart recipients (NYHA Class III-IVH (Group I: ischemic cardiomyopathy [n=13, 53 + 3 /rs, 75 + 9 kg, 1.9 + .1 m² BSA], Group II: primary ardiomyopathy, [n=5, 39 + 21 yrs, 68 + 16 kg, 1.8 - 2 - 2 PSA] .3 m² BSA]) were premedicated with lorazepam (10-33 ncg/kg), induced with fentanyl (13 + 8 mcg/kg, Group I) or ketamine (1 + .3 mg/kg, Group II) and succinylcholine (1 mg/kg), sterilely intubated (cricoid pressure) paralyzed with vecuronium (.mg/kg), anesthesia maintained (both groups) witifentanyl (25 + 16 mcg/kg) and isoflurane (0.25-0.75) incrired and mechanically contileted (PFFP = 5.53) inspired) and mechanically ventilated (PEEP = 5 ca 120). Heart rate (HR, bpm), mean aortic pressur MAP, mmHg), mean pulmonary artery pressure (MPAP mHg), central venous pressure (CVP, mmHg), pulmoniry artery diastolic pressure (PAPP, mmHg), thermolilution cardiac index (CI, L/min/m² BSA), systemi ind total pulmonary vascular resistance indice SVRI, TPVRI [normal: 350 + 80 dynes sec cm⁻⁵m²]) itroke volume index (SVI), Temp (T°C), ABG, Hct i02, PAo2 (mmHg) and A-aDo2 (mmHg) were measured o alculated (standard equations (2)) preoperativel rom catheterization data or invasive monitoring (Patheter) after induction until bypass After atheter) after induction, until bypass. Afte nduction, nitroglycerin (NTG), nitroprusside (NTP ind dobutamine (DBT) (mcg/kg/min) were administered augment CI and decrease SVRI and TPVRI. Analysis variance and Pearson regression Epistat®) were used to establish significance o orrelation.

nesthesia and mechanical ventilation did not affecte operative (I of 2.2+.6, HR 89+19, MAP 89+12 VP 13 \pm 8 and MPAP 35 \pm 7 or TPVRI 1429 \pm 594 or ither group (Fig. 1). In 7 patients of Group I and of Group II (responders) DBT (4 \pm 6) and NTG and ITP (1 \pm 1) caused a gradual rise in CI, in all atients 48% (p < .01), Group I 36% (p < .02) and incorp II 89% (p=.07) from postinduction CI (2.3 \pm .8 \pm .5 \pm .8 and 1.9 \pm .6 respectively) and SVI rose 26% n Group I and 80% in Group II from postinduction VI of 32 \pm 12 and 21 \pm 6 respectively (p < .05) Fig 1). Concurrently, SVRI and TPVRI decreased incorp I 34% and 50% (p < .02), Group II 39% (N.S. and 55% (p < .01) respectively. from postinduction nesthesia and mechanical ventilation did not affecnd 55% (p < .01) respectively, from postinduction alues (Group I [SVRI 2527 + 975], [TPRVI 1260 - 21] and Group II [SVRI 2793 + 1207], [TPRVI 1658 -70]). Percent rise in CI in both groups correlated p < .01, R=.81) with percent fall in SVRI and TPVR Fig 2). Postinduction MAP (84 + 12), HR (83 + 19) nd CVP (16 + E) did not change during CI augmentation, whereas MPAP decreased 32% only in Group

responders (p < .02) from post induction MPAP 39 + 12 mmHg. In 6 Group I patients (nonresponders) (CI 2.9 ± .7, SVRI 2200 ± 912, TPVRI 797 ± 362), transplanted for malignant arrhythmias and/or intractable angina, in whom CI was judged satisfactory and its augmentation was not aggressively pursued (less inotropes and dilators), CI augmentation (6%) and TPVRI reduction (20%) were not significant.

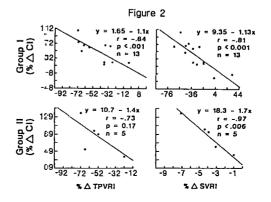
Discussion. Anesthesia and mechanical venti-lation did not adversely affect PVI (TPVRI) of heart recepients. Furthermore, PVI (TPVRI) can be decreased before bypass in 60% of recipients with pump failure to lower values than those preoperatively estimated by using high FiO2 and pulmonary vasodilator agents. In the remaining recipients with indication for transplantation other than pump failure, PVI reduction is not necessary.

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Figure 1 DST. NOO NOD CI Λl 4000 2000 3500 1500 3000 SVRI TPVRI 1000 2500 p<.01 -- *TPVRI* -- *SVRI* 500 2000 J₁₈₀₀



Title: PROPOFOL BLOOD CONCENTRATIONS REQUIRED TO SUPPLEMENT NITROUS OXIDE ANESTHESIA

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Introduction. Propofol (Diprivan) is a new intravenous (iv) sedative-hypnotic which can be used as an adjunct to nitrous oxide for induction and maintenance of general anesthesia. Its pharmacologic profile consists of a rapid onset and distribution, high clearance rate, and short elimination half-life with rapid recovery. These properties suggest that a close relationship may exist between propofol's blood concentration and the intensity of its clinical effect. In this study, we determined the blood concentrations of propofol required to suppress clinical responses to major (intra-abdominal) and non-major (body surface) surgical stress. Propofol blood levels were also correlated with specific recovery indices.

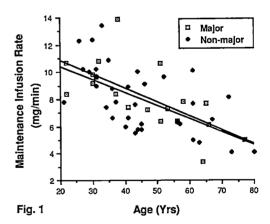
Methods. Sixty, consenting, ASA I-III, adult patients undergoing non-major or major procedures The study was approved by the were studied. Preoperatively, Institutional Review Board. patients were administered a battery of psychometric tests (e.g., Trieger, p-deletion, and sedation analog scales). Anesthesia was induced with meperidine, 1 mg/kg iv, and propofol, 2 mg/kg iv. Following tracheal intubation, and sedation analog scales). maintained with nitrous oxide, 70% in oxygen, and an infusion of propofol (0-20 mg/min) that was varied according to the presence (inadequate anesthesia) or absence (adequate anesthesia) of somatic and/or autonomic responses (e.g., movement, diaphoresis, lacrimation, heart rate or blood pressure changes > 20% of baseline values). Bolus doses of propofol, 10-2) mg iv, were administered for rapid control of patient responses followed by an increase in the infusion rate. Postoperatively, times to awakening and orientation were noted, and psychometric tests were repeated at 30 min intervals. Peripheral venous blood samples were obtained intraoperatively and up to 8 h postoperatively. Samples were analyzed for whole blood propofol levels using HPLC. Propofol concentrations were correlated with clinical signs of anesthetic depth as well as with recovery indices. The effective concentration at which 50% (EC50) and 95% (EC95) of patients achieved specific recovery endpoints were calculated and analyzed with sigmoid function modelling. Statistical analysis included linear regression, t-test, and Mann-Whitney ranksum test. Values are expressed as mean + S.D

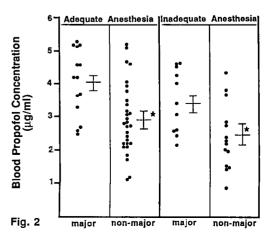
Results. Demographic data were similar for the two treatment groups (age, 45 ± 15 yrs; weight, 70 ± 19 kg). Patients who underwent major procedures received more propofol (1605 ± 511 vs. 619 ± 272 mg, p<0.01) over a longer period of time (175 ± 51 vs. 67 + 32 min, p<0.01) than patients in the non-major group. The mean propofol infusion rate decreased in an age-related fashion (fig. 1). Patients undergoing major (vs. non-major) operations required higher blood propofol levels to prevent responses during surgery (4.01 ± 1.01 vs. 2.97 ± 1.07 ug./ml, p<0.01). Correspondingly, blood propofol levels at which responses to surgical stimuli occurred were higher in major (vs. non-major) surgical patients (3.46 ± 0.95 vs. 2.39 ± 0.99 ug/ml, p<0.05) with considerable overlap between all groups (fig. 2). There was a positive

correlation between intraoperative propofol blood concentration and the maintenance infusion rate (r=0.72, p<0.001). The EC50 and EC95 values (ug/ml) for the recovery indices are:

EC50 1.07 0.95 0.43 Trieger Sedation 0.52 0.46 0.20 0.20 0.22

Discussion. A continuous, variable-rate infusion of propofol improves the anesthetist's ability to titrate this rapid, short-acting anes-The age-related decrease in the maintenance propofol requirement would suggest that the elderly are more sensitive to propofol and/or display a decreased propofol clearance rate. Pharmacodynamic analysis of intraoperative propofol concentrations suggests that adequate blood levels of propofol are dependent upon the type and severity of the surgical stimulus and that a large degree of interpatient variability exists. Similarly, recovery of psychomotor skills occurred over a wide propofol concentration range (0.1-0.9 Thus, to maintain satisfactory anesthetic conditions and to provide for a rapid recovery of consciousness and psychomotor function, the propo-fol infusion should be varied according to individual patient responses to surgical stimulation.





Title: INTRATHECAL MORPHINE REDUCES THE MINIMUM ALVEOLAR CONCENTRATION OF HALOTHANE IN MAN.

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Opiates injected either intrathecally or Introduction: epidurally produce profound and prolonged analgesia. In addition to their established role in the treatment of postoperativepain, intraspinal narcotics might also be useful as adjuncts to general anesthesia. Previously, we demonstrated that the intrathecal administration of morphine in rats significantly reduced anesthetic requirement. The present study was designed to determine whether intrathecal morphine would decrease anesthetic requirement in humans.

Methods: Following approval from the Committee on_ Human Research, and after obtaining appropriate written informed consent, sixteen patients undergoing major abdominal gynecological surgery were studied. All patients were classified as ASA I or II physical status.

Subjects were divided randomly into two groups. Prior to the induction of anesthesia, subjects in group A received an intrathecal injection of 0.75 mg preservative-free morphine sulfate. Subjects in group B received the same dose of morphine sulfate administered intramuscularly. No other

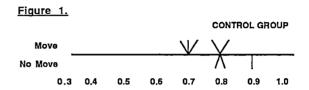
premedication was given.

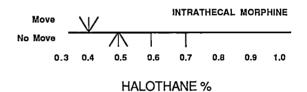
Anesthesia was induced with halothane, oxygen and nitrous oxide. After an adequate depth of anesthesia was obtained, succinylcholine was administered, the trachea was sprayed with 4 ml of 4% lidocaine, and a cuffed endotracheal tube was passed. Nitrous exide was discontinued, a 5 liter/min flow of oxygen continued, and the level of halothane adjusted to obtain a pre-selected end-tidal concentration. The concentration selected was adjusted to account for differences in patient age on MAC.² Ventilation was controlled to obtain an end-tidal PaCO2 between 27 and 34. Gas samples, obtained from a catheter at the endotracheal tube connection site, were analyzed by a mass spectrometer. Halothane and CO2 concentrations were displayed on a strip chart recorder and the wave forms were examined to insure that a plateau phase had been obtained. A single standardized halothane tank was used to calibrate the mass spectrometer prior to each trial. The pre-selected end-tidal concentration was maintained for a minimum of 20 minutes prior to the skin incision. A nerve stimulator was used to insure that, at the time of skin incision, residual succinylcholine paralysis was no longer present. The determination as to whether or not gress purposeful movement had occurred was made by an observer unaware of the group designation of the subject. Heart rate and blood pressure were recorded immediately before and one minute after skin incision.

End-tidal concentrations were chosen using a modification of Dixon's method for sequential sampling of quantal-response data.³ This sampling technique uses the results of each trial to dictate the dose level sampled on the following trial. Thus, in the present experiment if a patient did not move at skin incision, the next patient in that treatment group was tested at a lower concentration of halothane. Conversely, if movement was observed, the next patient was tested at a higher concentration. The MAC of halothane for both groups was calculated using the method of Dixon. The two groups were compared using Student's t test with p<0.05 considered significant.

Results: Intrathecal administration of 0.75 mg morphine sulfate produced a significant reduction in anesthetic requirement (figure 1). The MAC of halothane for the control group and the

intrathecal group was 0.78% and 0.46%, respectively. Thus, the MAC for the group that received 0.75 mg intrathecal morphine was approximately 60% of that determined when the same dose was administered intramuscularly.





There were no significant differences between the two groups with respect to age, temperature, pre-incision blood pressure, end-tidal CO2 duration of anesthesia, or time from injection or intubation to incision.

<u>Discussion</u>: Intrathecal narcotics produce analgesia by inhibiting spinal nociceptive transmission. This effect is mediated by a direct action at opiate receptors within the the dorsal horn of the spinal cord, and does not appear to be dependent upon an action at opiate-sensitive sites in the brainstem.

The results of the present experiment demonstrate a significant reduction in MAC with the intrathecal administration of morphine. MAC has been shown not to vary with stimulus intensity once a certain "supramaximal" level has been achieved. Thus, intrathecal morphine most likely inhibited afferent nociceptive input such that the stimulus was no longer 'supramaximal''.

This information has important clinical as well as theoretical implications. It supports a useful role for spinal narcotics as adjuncts to volatile anesthetics.

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TITLE:

SMALL INCREASES IN PLASMA GLUCOSE (50%) AGGRAVATE NEUROLOGIC OUTCOME AFTER SPINAL CORD ISCHEMIA

IN THE RABBIT

ALITHORS:

JC Drummond, M.D., F.R.C.P.(C), SS Moore, B.S.

AFFILIATION: The Departments of Anesthesiology (Neuroanesthesia Research) of the University of California, San Diego

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INTRODUCTION: We have previously demonstrated that an elevated plasma glucose (PG) concentration results in a poorer neurologic outcome following temporary spinal cord ischemia (SCI). However, in our previous study, PG elevation was accomplished with an IV bolus of hypertonic dextrose and the elevation of PG vs the control group was substantial (130 mg/dl). This study sought to determine whether more modest PG elevation achieved in a manner more analagous to common clinical events would influence neurologic outcome. METHODS: Ischemia of the distal spinal cord was produced by temporary balloon occlusion of the aorta in the New Zealand White rabbit. Sixteen rabbits of either sex weighing 2.6-3.1 kg were allowed water ad libitum but were otherwise fasted for 21 hrs prior to study. Anesthesia was induced with halothane, administered initially in a plexiglass box and subsequently by mask. A teflon catheter was place in a marginal ear vein and a 4 Fr. balloon tipped angiography catheter (Critikon) was positioned transfemorally in the aorta with the tip 0.5-1.5 cm distal to the left renal artery. Blood pressure was recorded continuously via the dye injection orifices the balloon the grant wound was which lay caudal to the balloon. The groin wound was infiltrated with 0.25% bupivicaine and the anesthetic was discontinued.

Five minutes thereafter, on an alternating basis, an IV infusion of either lactated Ringer's solution (LR) or 5% dextrose in water (D5W) was started at a rate of 7ml/kg/hr. The infusion continued for 90 minutes at which time ABG's, PG, osmolality (OSM), hematocrit (HCT), mean arterial pressure (MAP) and (HR) were determined. The infusion was then discontinued and the aorta was occluded. Twelve minutes later the balloon was deflated and one minute thereafter the measurements were repeated. aortic catheter was then removed. Neurologic status was graded daily for three days by a blinded observer according to a 5 point scale: 0) Paraplegic-no lower extremity movement; 1) Paraparetic-flicker of movement only; 2) Paraparetic-good antigravity strength but cannot hop; 3) Hops-but not normal; 4) Hops normally. The rabbits received daily antibiotic (Kefzol, 25mg/kg, IM) and urine was expressed manually as required. The neurologic scores at Day 3 were compared using a rank-sum technique (Mann-Whitney test). Student's t tests for paired and unpaired data were used for the within and between groups comparisons of all other data.

<u>RESULTS:</u> There were no differences between the LR and D5W groups prior to aortic occlusion with the exception of PG which was an average of 46mg/dl greater in the D5W group (179±15 (SE) vs 133±4, p<.01) (see Table). One minute post occlusion, PaCO, had decreased significantly in both groups (p<.002). In the D5W group, post-occlusion MAP was significantly less (p<.02) than the pre-occlusion value. Post occlusion MAP's did not differ significantly between the D5W and LR groups(78±5 vs.) significantly between the D5W and LK groups (78 ± 5) VS 94 ± 8 mmHg, p<.08) although a trend toward lower pressures in the D5W group seems apparent. PG decreased during the occlusion period in the D5W group (p<.04) and increased in the LR group (p<.04). Neurologic outcome was significantly (p<.005) poorer in the D5W group (See Figure).

DISCUSSION: Previous investigations which have indicated that an elevated PG may aggravate the effects of a period of CNS ischemia have frequently entailed dramatic elevation of PG and have commonly accomplished it by bolus administration of hypertonic (50%) dextrose. In the present study, an adverse neurologic effect following SCI occurred when a modest elevation (less than 50mg/dl) of PG was produced by slow infusion of an isotonic dextrose solution. It should be noted that, the apparently lower post ischemic MAP values observed in the dextrose treated animals may have contributed to the neurologic result. However, a similarly deleterious effect of moderate PG elevation was recently reported in a primate study of cerebral ischemia², and together these investigations further support the suggestion that dextrose containing solutions should be administered for a specific clinical purpose, especially when their is a risk of CNS ischemia.

66:S43, 1987. 2. Lanier WL, et al. Anesth Analg 66:39-48, 1987.

	D5'	w	LR
	PRE OCC	POSTOCC	PRE OCC POST OCC
PG	179±15#	154±8*	133±4 146±5*
MAP	94±3	78±5*	96±5 94±8
HR	248±12	295±13*	255±11 280±11*
рН	7.43±.03	7.41±.03	7.36±.02 7.37±.03
PCO2	28±1	22±1*	26±2 22±1*
PO2	87±1	94±2*	90 <u>±</u> 2 96±2*
HCT	40±1	41±1	39±1 41±1
OSM	284±2	286±2	282±1 283±1

<u>TABLE.</u> Physiologic data prior to (PRE OCC) and following (POST OCC) 12 minutes of infra-renal aortic occlusion. See text for abbreviations. * indicates a statistically significant (p<.05) within group difference between the pre and post occlusion values. # = p<.01 vs PRE OCC PG in LR group.

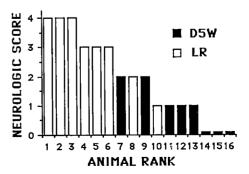


FIGURE. Neurologic score after spinal cord ischemia. The rabbits have been ranked according to neurologic function 72 hours post ischemia; 4 indicates normal function and O represents complete paraglegia.

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Title:

EFFECT OF MEMBRANE OXYGENATORS ON SUFENTANIL BLOOD LEVELS DURING CARDIOPULMONARY BYPASS

Authors:

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Introduction. High doses of sufentanil $ar\epsilon$ commonly used either as the sole or primary anesthetic agent during cardiovascular surgery. F complete understanding of the pharmacokinetics of sufentanil is crucial to guide rational clinical use of the drug. Studies have documented the abrupt and marked decline in serum concentrations that occurs following initiation of cardiopulmonary bypass (CPB). Philbin et. al. 2 studied serur levels during CPB and concluded that the decrease was primarily the result of hemodilution. The CPE circuit for these studies included a bubble oxygenator system. Membrane oxygenator systems are now more commonly used during CPB. They are cap able of absorbing significant amounts of sufentanil3. However, these in vitro studies were done without first coating the membrane with albumin. This process is required for optimum clinical function of the oxygenator4. Albumin coating could significantly alter the absorption of sufentanil. The following study was designed to letermine the relative contribution of factors other than hemodilution to the decrease in serum sufentanil concentration. In addition, we will letermine if different types of membrane effects.

Methods. Patients scheduled for elective CABG urgery gave their consent to this study as ap-roved by the Institutional Review Board. All atients received their usual morning doses of nti-anginal medications. Morphine (0.1 mg/kg, IM) nd scopolamine (0.004 mg/kg, IM) were given one our prior to induction. Following the application f standard monitors, each patient received an ntravenous infusion of 5 $\stackrel{\cdot}{\text{mcg/kg}}$ of sufentanil itrate over five minutes. When the patient became nresponsive to stimulation, intubation was chieved following administration of pancuronium 0.1 mg/kg). Maintenance of anesthesia was ontinued with a second dose of sufentanil citrate 5mcg/kg over ten minutes) and 100% oxygen with nflurane supplementation if required. Serial lood samples were drawn every 20 minutes from a adial artery cannula until 5 minutes after nitiation of CPB. Plasma sufentanil concentra-ions were determined using a radioimmunoassay that as been shown to be both specific and sensitive to .3 ng/ml. Patients were divided into 2 groups. he CPB circuit in group A utilized a SciMed II ambrane oxygenator (Life Systems Inc.) while group utilized a Maxima hollow fiber oxygenator Johnson & Johnson cardiovascular).

Results. Pre-CPB serum concentrations were used construct plasma decay curves. The terminal hase of the curve was extrapolated to determine to volume of distribution (VdB) and to determine to concentration five minutes following initiation f CPB (Ccalc). The amount of drug remaining in the body (M) was then determined. A second volume f distribution (V'd) was calculated by dividing M / the measured serum concentration at that time.

The results are summarized in the following table:

OXYGENATOR	Sc1Med	Fiber
n	5	3
V _{dB} (L) Ccalc (ng/ml) M (ng)	156 <u>+</u> 13	146+29
Ccalc (ng/ml)	1.29 <u>+</u> .11	0.86±.36
M (ng)	200 <u>+</u> 22	146 <u>+</u> 78
Cmeas (ng/ml)	0.90 <u>+</u> .04	0.66±.14
Vid (L)	226 <u>+</u> 29	184 <u>+</u> 64
Values expresse	ed as Mean	+ SEM

There is a significant (p<0.05 paired t-test)difference between Ccalc and measured serum concentrations, following initiation of CPB only for group A. V d is 42.6 \pm 11.3% greater than VdB for group A and 21 \pm 22% for group B.

Discussion. Multiple studies have documented the decline in serum concetrations of sufentanil and other anesthetic adjuncts drugs following initiation of CPB. CPB is associated with multiple factors which can alter the pre-bypass pharmacokinetics. Foremost among these is the massive hemodilution which occurs but CPB is also associated with changes in serum protein concentrations, protein binding, cardiac output, blood flow distribution, perfusion pressure and temperature. All of these factors have been suggested to play a role in the similar alteration of fentanyl kinetics seen in this clinical setting. Although closely related to fentanyl, sufentanil has a greater lipid solubility and is more highly protein bound. As such, the relative contribution of each of the factors discussed above for fentanyl will differ for sufentanil.

The marked changes in volume of distribution seen in this study are too great to be accounted for by hemodilution alone. These results are consistent with a substantial uptake of sufentanil by the CPB circuit. These data do not demonstrate that priming the oxygenator membrane with albumin decreases the drug binding. In addition, despite the small number of patients there is evidence that the effects of CPB on the kinetics will vary depending on the type of oxygenator used.

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Title: CARBAMAZEPINE THERAPY AND NEUROMUSCULAR BLOCKADE WITH ATRACURIUM AND VECURONIUM

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Introduction: Resistance to pancuronium has been demonstrated in patients receiving carbamazepine. ¹ The resistance was characterized by a more rapid recovery from neuromuscular blockade after an intubating dose of pancuronium. In patients receiving phenytoin, a similar effect has been observed after administration of pancuronium, metocurine, and vecuronium, but not with atracurium.²⁻³ To help elucidate the mechanism of this phenomenon, and to further evaluate its scope, we studied the duration of neuromuscular blockade after vecuronium and atracurium in patients receiving carbamazepine.

Methods: Informed consent was obtained using a protocol approved by the Institutional Review Board. We studied thirtyfive patients undergoing craniotomy for tumors, seizure focus excision or cerebrovascular surgery. Patients' ages ranged from 15 to 45 yrs. Premedication consisted of diazepam 10 mg p.o. or midazolam 3 mg i.m. one hour prior to surgery. Patients with renal, hepatic, pulmonary, cardiovascular, or neuromuscular disease were excluded. Group I patients were on chronic carbamazepine therapy and Group II patients received no anticonvulsants. Serum carbamazepine levels were in the therapeutic range prior to surgery. Anesthesia was induced with thiopental 4-5 mg/kg i.v. and fentanyl 8-10 μ g/kg i.v. or sufentanil 1 μ g/kg i.v. Vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg were administered to facilitate endotracheal intubation. Anesthesia was maintained with nitrous oxide 70%, oxygen 30%, and 0.25% end-tdal halothane, measured using mass spectrometry. Patients were monitored with radial artery catheters, ECG, mass spectrometry, and an esophageal temperature probe. Heating pads and a cascade humidifier were used to maintain temperature above 35°C. The PCO2 was maintained by mechanical ventilation at 25-30 mmHg. Oxacillin 1 gm was given i.v. to every patient after induction of anesthesia. The ulnar nerve was stimulated indirectly near the wrist with a Puritan-Bennett Datex 221 Neuromuscular Transmission Monitor. The device delivers 100 µs square wave supramaximal train-offour impulses at a rate of 0.2 hz via surface electrodes. The evoked adductor pollicus response was recorded as the integrated electromyogram (EMG). The time to 25, 50, 75 and 90% recovery of baseline EMG activity was recorded and the recovery index calculated as the difference between 75 and 25% recovery. The recovery times after the two neuromuscular blockers were compared with controls using the non-parametric Wilcoxon rank sum test with a Eonferroni correction for multiple comparisons. A value of p<0.05 was considered statistically significant.

Results: There was no statistically significant difference in age between control and carbamazepine patients. At each level, the time required for carbamazepine patients to recover from neuromuscular blockade after vecuronium was significantly shorter than for controls. There was no difference between control patients and those receiving carbamazepine in recovery times after atracurium. Recovery index was also significantly shorter for carbamazepine patients compared with controls for vecuronium $(7\pm 3 \text{ vs.} 17\pm 9, p < 0.025)$, but no difference existed for atracurium $(8.5\pm 2 \text{ vs.} 8\pm 2, \text{ NS})$.

<u>Discussion</u>: This study indicates that patients on carbamazepine therapy recover faster from a vecuronium, than from an atracurium neuromuscular blockade. These results are similar to those of Ornstein *et al.*, who showed that patients receiving the anticonvulsant phenytoin were resistant to vecuronium-induced neuromuscular blockade but not to that of atracurium.³ Alderdice

et al.⁴ have shown evidence of a direct effect of carbamazepine on an *in vitro* frog motor endplate where carbamazepine decreased release of neurotransmitters and diminished post-junctional sensitivity to acetylcholine. This does not explain the present findings but suggests that the neuromuscular relaxants and anticonvulsants may compete for the same site(s) on the neuromuscular junction. As previously suggested,⁵ atracurium may be more tightly bound at the neuromuscular junction than either vecuronium or pancuronium. This may account for the anticonvulsants' lack of antagonism on the effect of atracurium. In summary, patients receiving phenytoin appear to have a resistance to neuromuscular blockade similar to that of patients on carbamazepine therapy.

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TIME TO PERCENT RECOVERY OF BASELINE TWITCH HEIGHT IN MINUTES (MEAN \pm SD)

	VECURONI	<u>UM</u>	ATRACURIUM			
C	Carbamazepine N=9	Control N=9	Carbamazepine N=8	Control N=9		
25%	25±7*	40±8	35±6	31±11		
50%	28±7†	47±11	40±6	35±11		
75%	32±9†	56±16	44±7	39±12		
90%	36±10 [‡]	60±18	47±7	42±13		
Recove Index		17±9	9±2	8±2		
Age (y	rs) 29±7	43±18	28±8	31±11		

*p<0.005 vs. control

 $\dagger p < 0.01 \text{ vs. control}$

 $^{\ddagger}p$ <0.025 vs. control

itle: MECHANISM OF VASOMOTOR CHANGES WITH ISSELURANE

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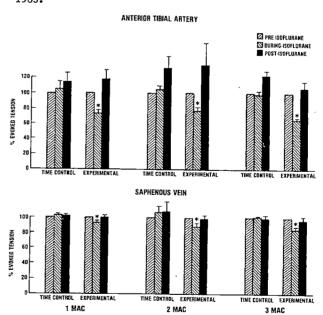
Introduction. Isoflurane has well known asodilator properties, producing significant ecreases in SVR, particularly in skeletal muscle nd cutaneous vascular beds. Using chronic nerve ecordings, dose-dependent decreases in sympathetic fferent tone have been demonstrated (1), but the there isoflurane decreases the response of blood assels to peripheral sympathetic nerve stimulation sunknown. The objective of this study was to camine the effects of isoflurane on the neuro-ascular junction in isolated canine peripheral teries and veins. This was accomplished by termining the response of isolated vascular rings transmural electrical stimulation (ES), and creasing concentrations of norepinephrine (NE) the tyramine.

Methods. Anterior tibial arteries and uphenous veins were harvested from pentobarbital nesthetized (30mg/kg, IV) mongrel dogs of either ex (20-35 kg). Three millimeter rings were 'epared, placec in jacketed tissue baths filled th Krebs Ringers bicarbonate solution aerated th 95% 0₂/5% CO₂, maintained at 37°C. Each ring s suspended by two stainless-steel hooks passed rough the lumen of the vessel with one hook tached inside the tissue bath, and the other nnected to a force transducer (FTO3) for connuous measurement of isometric tension. Two atinum electrodes placed parallel to the rings re used for ES. Electrical impulses consisted square waves (13V, 2 ms, 2Hz, 10min) provided a direct current power supply and a switching ansistor triggered by a Grass stimulator. oflurane was added to the gas mixture from a pper kettle with metered flow and its conntration in the tissue baths confirmed by gas romatography. Each vessel was placed at the timum point of its length-tension relationship ior to the start of the experiments. Experiments cluded measurement of the response of the vessels increasing frequencies of ES, determination of se-response curves to NE and tyramine prior to, ring and following exposure to isoflurane. asurement of the effect of isoflurane on resting nsion was also made. Each isoflurane-treated ssel was paired with a time control. Analysis data was done with paired t-tests. p < 0.05 s considered significant.

Results. In both vessels isoflurane (1, 2, d 3 MAC) produced significant decreases in sponse to electrical stimulation (See Figure). eater decreases in tension were observed in the terial preparations. Isoflurane did not alter sting tension, and did not alter the response exogenous NE in either arteries or veins. oflurane (3 MAC) also did not alter the response tyramine in the veins.

Discussion. Transmural electrical stimulation causes the release of endogenous NE from vascular sympathetic nerve endings $\tilde{b}y$ a calcium-dependent mechanism, while tyramine causes release of NE by a calcium-independent mechanism. In the present experiments isoflurane caused significant decreases in response to ES but not to tyramine or to exogenous NE. This suggests that isoflurane interfers with calcium-dependent NE release but does not effect calcium-independent NE release or NE receptor senstivity of the vascular smooth muscle. The greater inhibition of the response to ES of arteries than of veins is consistent with the clinically observed large decreases in SVR and modest venodilator properties of this anesthetic. These data suggest that part of the vasodilation caused by isoflurane is the result of its decreasing calcium-dependent NE release from vascular adrenergic nerve endings during sympathetic nerve activity.

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Effect of 1, 2, and 3 MAC isoflurane on 2 Hz sustained ES in paired arteries and veins. Results expressed as percent of the maximal evoked tension pre-isoflurane treatment. Data are mean + SEM. *=p<.05.

Title:

BILATERAL INTRAPLEURAL INTERCOSTAL NERVE BLOCK

Authors:

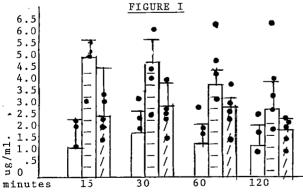
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Introduction: Unilateral intrapleural intercostal nerve block provides pain relief in a variety of clinical situations. 1,2,3,4 This study is to evaluate the peri-operative pain relief of bilateral intrapleural intercostal nerve block (BIINB) in midline and across midline abdominal surgical interventions.

Method: With institutional approval and patients' consent bilateral intrapleural catheters were inserted after surgery using Mancao* dual-carnula system at the angle of the 8th rib 10 cm. from midline. Bupivacaine with epinephrine (BE) was administered in each side as follows: (a) 20 cc of 0.5%(b) 30 cc of 0.75%, and (c) 20 cc of 0.75%. Arterial blood levels of bupivacaine were determined 15, 30, 60 and 120 minutes using gas chromatography. 5 In 16 patients undergoing similar surgery (control group) we compared the frequency of narcotics administered 4 days peri-operatively, the post operative hospital stay and other variables. Student T test and analysis of variance were used when applicable. Statistical significance was obtained at P< 0.05.

Results: BE 20 cc 0.5% was ineffective in 3 patients and 30 cc 0.75% was toxic in 2 of 5 patients. BE 20 cc 0.75% was effective with no toxicity in 18 patients: cholecystectomy 6, gastrectony 5, aortic surgery 2, nephrectomy 2 and expl. lap. 3. The two groups were comparable and the changes in blood pressure and pulse rate in recovery unit were insignificant. Fig. 1 shows bupivacaine blood levels & Table 1 shows other findings.



Bupivacaine blood levels: individuals = •, mean $= \square$ stand deviation = T

0.5% BE G-1 20 cc (n=3)

0.75% BE G-2 30 cc (n=4) 0.75% BE G-3 20 cc (n=5)

Differences bet. G1 and G2 were all significant.

Differences bet. Gl and G3 were all insignificant.

Differences bet. G2 and G3 were only significant at 15 and 120 minutes.

TABLE I FREQUENCY OF NARCOTICS USED, P/O HOSPITAL STAY, DURATION OF PLEURAL CATHETERS AND DURATION OF 1st, 2nd AND 3rd DOSE OF BE.

		n	HEAN	.SD .	MIN	MAX	RANGE	t/p_
IARC.	CON- TROL	16	20.0	5.02	12	32	20	10.9/0.0003
FREQ.	BII	18	3.38	1.55	1	6	5	0003
HOSP.	O H		21	13.5	10	59	49	1.7/0.108
P/0 SJ	BII		14.2	6.4	7	33	26	108
PC	ATION (HRS)	18	54.7	57.08	19	251	232	pleural cath.
	ATION 1st E	18	16.0	5.14	8	26	18	
	ATION 2nd E	12	22.3	6.1	9	30	21	*5.25/ 2.0
1	ATION 3rd E	8	27.3	6.1	22	36	14	*0.98/ 0.39

x Statistically significant difference. * Difference from 1st dose, not significant.

Discussion: BIINB provides profound, prolonged and repeatable pain relief. We recommend using dosages of 20 cc 0.75% BE in each side. BIINB decreased significantly the frequency of narcotics administered in the 1st 4 days after surgery.

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itle:

LABETALOL VS. NITROPRUSSIDE FOR DELIBERATE HYPOTENSION: EFFECTS ON SYSTEMIC HEMODYNAMICS AND ARTERIAL OXYGENATION

uthors:

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Labetalol is a drug that blocks both alpha and sta adrenergic receptors. It has been advocated or deliberate hypotensicn during halothane testhesia. However, its hemodynamic profile is to twell defined. We compared its effects on modynamics and arterial blood gases with those of dium nitroprusside.

Methods. Twenty consenting adults were enrolled the study which was approved by the institution. 1 patients were scheduled for major procedures quiring deliberate hypotension to decrease traoperative blood loss. They were randomly signed to receive either labetalol (n=10) or troprusside (n=10). Demographic data were mparable in both groups. They were premedicated th oral diazepam (0.1 mg/kg) and intramuscular rphine (0.1 mg/kg). Anesthesia was induced with iopental, 5 mg/kg, followed by succinylcholine, mg/kg, for endotracheal intubation. Anesthesia s maintained with enflurane (1-2%, inspired), 0:0, (3:2 L/min), and curare, in doses sufficient block neuromuscular transmission. Intravascular theters were inserted prior to induction of esthesia for monitoring arterial and central nous pressures, and for blood sampling. potension was induced, prior to the surgical potension was induced, prior to the suspension, using either incremental doses of travenous labetalol or an infusion of troprusside (0.01% solution). Labetalol ven in an initial dose of 20 mg and the response sessed after 3-5 min. Further doses (10-20 mg :rements) were administered until a mean arterial essure of 50-55 mmHg was obtained. A similar essure was obtained in the nitroprusside group by justing the rate of infusion. Hemodynamic surements and arterial blood samples (for PO2, 2, and pH) were obtained before hypotension, 60 min after hypotension was achieved, before nd closure (labetalol group) or after mination of infusion (nitroprusside group).
diac output was measured in duplicate by dye ution, intravascular pressures were transduced, heart rate obtained from the ECG. Postrative assessments were made 2 and 24 hours

er operation.

Results. Hypotension produced by labetalol or roprusside was primarily related to a decreased temic vascular resistance (P < 0.01). However, re were differences between the hypotension duced by the two compounds. Nitroprussideuced hypotension was rapid in onset, associated has significant increase (P<0.05) in heart rate cardiac output, and a rapid return of blood soure to control values upon discontinuation of usion. There was rebound hypertension in three ients. After labetalol, the reduction of source was slow in onset; a mean arterial

ssure of 50-55 $\,$ mmHg was achieved in 14 min age 11 to 21 min). Cardiac output and heart

rate were not significantly changed during labetalol-induced hypotension. Blood pressure returned gradually to control after the termination of anesthesia. Rebound hypertension was not observed.

Arterial blood PO was significantly decreased (P<0.05) in the two groups. Blood loss was not significantly different between the groups. There were no postoperative sequelae in either group.

Discussion. Our results demonstrate that labetalol is an effective hypotensive agent during enflurane-N₂O anesthesia. Its beta-adrenergic blocking activity (both beta 1 and 2) is evident by the absence of tachycardia and unchanged cardiac output in response to a decreased systemic vascular resistance. This is in contrast to nitroprusside, a direct-acting vasodilator, which is associated with reflex activation of the heart rate and cardiac output.

cardiac output.

The qualities of hypotension produced by labetalol differ from those of nitroprusside. Labetalol has a slow onset of action, and does not require adjustment of the rate of infusion. Once hypotension is achieved, it is maintained for 3-6 hours. After termination of anesthesia, blood pressure returns to preoperative values in 13 to 22 minutes, without a rebound increase in pressure.

Our results differ from those published by Kaufman and Scott et al. These authors induced hypotension with smaller doses (25 mg) of labetalol during halothane anesthesia. We found that the dose requirements for labetalol ranged from 90 to 230 mg to achieve a mean arterial pressure of 50-55 mmHg. This discrepancy might be related to a different patient population and the anesthetic agents employed.

Labetalol is a useful hypotensive drug during general anesthesia for procedures requiring several hours of deliberate hypotension.

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Title: EFFECT OF THE FASTING INTERVAL ON GASTRIC PH AND VOLUME IN CHILDREN

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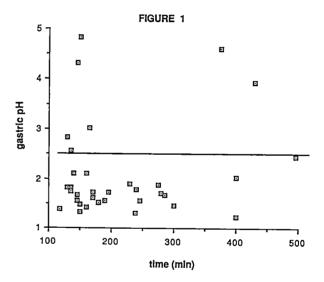
Introduction: The literature presents conflicting data concerning the preoperative fasting period for pediatric patients. 1,2 To more accurately define preoperative fasting regimens in pediatric patients, we determined the effects of the fasting interval on the gastric pH and gastric fluid volume in pediatric patients.

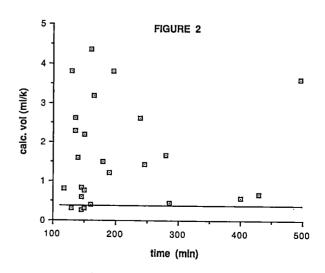
Methods: After approval from our Committee on Human Research, informed written consent was obtained from thirty-five pediatric patients and/or their parents to participate in a prospective randomized blinded study. All patients were unpremedicated, ages 1 to 18 years, ASA I or II, with no evidence of gastrointestinal disorder, and scheduled for elective surgery. Each child was randomized to receive 2 ml/kg of water orally at 2, 4, or 6 hours before the scheduled surgery. All patients were supine and horizontal before induction of anesthesia. After an intravenous induction and endotracheal intubation, an orogastric tube was inserted into the stomach. The position of the tube was confirmed by injecting several ml of air and auscultating over the epigastrium. An aliquot of gastric fluid (2-15 ml) was aspirated through the tube and 2 ml of the aspirate was retained for pH determination. Two mg/kg of sulfobromophthalein sodium (BSP), a nonabsorbable water soluble marker dye in a 5% solution, were injected into the stomach and flushed with the excess aspirated gastric fluid. Air was then injected to flush the tube. The marker dye was thoroughly mixed with gastric fluid. The stomach contents were then aspirated as completely as possible. The volume of gastric aspirate was measured in a graduated syringe. Two ml of the latter aspirate were retained for analysis of the BSP concentration. The pH was determined using a radiometer PHM62 standard pH meter calibrated with three standard buffer solutions: pH 7.0, 4.01 and 1.0. BSP concentrations were determined by colorimetry using a Gilford Stasar III Spectrophotometer.

Results: Gastric fluid was obtained in 34/35 patients. We found that 79% patients had a gastric pH (mean \pm SD) less than 2.5 (2.10 \pm 0.92) which was independent of the fasting interval (Figure 1). Gastric volumes as determined by the BSP dilution technique were significantly greater than the volumes of gastric aspirate (t-test, p < 0.05). Gastric volumes (by BSP dilution) were greater than 0.4 ml/kg in 88% of the patients (1.68 \pm 1.3 ml/kg) independent of the fasting interval (Figure 2). Both gastric pH < 2.5 and gastric volume > 0.4 ml/kg were present in 76% of patients.

Discussion: The results of this study demonstrate that fasting intervals between 2 and 6 hours do not protect pediatric patients from gastric pH < 2.5 and gastric volumes > 0.4 ml/kg. This suggests that at present, most fasting pediatric patients undergoing elective surgery are at risk for serious pneumonitis following aspiration of gastric contents.

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S60 ANESTH ANALG 1988:67:S1-S266 ABSTRACTS

HEMODYNAMIC EFFECTS OF NIMODIPITE ADMINISTERED TO CATS FOLLOWING Title: RESUSCITATION FROM CARDIAC ARREST

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Introduction: In recent years much interest has been focused on methods of attenuating neurologic deficits occurring in patients successfully resuscitated from cardiac arrest. It has been suggeste≡ that a group of drugs known as calcium entry blockers may have beneficial effects upon neurologic outcome when administer following an episode of complete cerebral ischemia. The calciu entry blocker nimodipine (N), has been shown to significantL improve post-ischemic neurologic outcome in non-cardiac arre-t nodels of complete cerebral ischemia (1,2). The effects of N ca systemic hemodynamics and neurologic outcome in a cardiaarrest model of complete cerebral ischemia have not previousL peen examined. In anticipation of studies of the effects of N upca. neurologic outcome, we have examined the hemodynamic effecs of N when administered to cats following resuscitation from :ardiac arrest

Methods: Fifteen colony bred cats weighing 2.0-2.9 kg were tudied with Institutional Review Board approval. Cats were mesthetized with halothane 4.0% inspired, followed bancuronium 1.0 mg iv to facilitate tracheal intubation. Halothare vas decreased to $\bar{1}.0\text{-}1.5\%$ inspired and nitrous oxide 65% i. xygen was added. Maintainance fluids consisted of norma aline at 4 ml/kg/h with pancuronium 0.5 mg/h. Ventilation and emperature were controlled to maintain normocarbia and ormothermia, respectively. EKG and EEG were monitoreontinuously using needle electrodes. Following local infiltratiovith 0.25% bupivacaine, cannulae were passed into the dista orta and right atrium (RA) via an incision in the left groin. The A cannula was placed with EKG guidance. A wire protruding .5 mm from the RA end of the cannula was left in place [alothane was discontinued and external stimuli were kept to ϵ uinimum for the next 30 min. Control (CONT) values of mear terial pressure (MAP), central venous pressure (CVP), heart rate IR), temperature, EKG, EEG, arterial blood gases (ABG), anc lood glucose were obtained. Ventricular fibrillation was inducec y passing a 20 volt, 60 Hz, AC current between the wire in the A and a needle placed percutaneously over the palpable cardiac apulse. AC current was maintained for up to one min entilation was stopped and the endotracheal tube occluded. Cats ith any spontaneous, perfusing heart beats following one mirere excluded from further study. After 13.5 min ventilation was sumed with 100% O2. Thirty seconds later closed chest cardiac assage (CPR) was initiated. Sodium bicarbonate 1 meq/kg, and inephrine 15 μg/kg iv were administered iv into the RA. After ie min of CPR a single 20 joule DC shock was given between ternal paddles. Sodium bicarbonate, epinephrine, and DC ock were repeated 3 times at one min intervals if needed. If the ird defibrillation was unsuccessful, lidocaine 1 mg/kg and opine 0.05 mg/kg were administered and DC shock repeated.

Resuscitation was considered successful when systolic blood essure was maintained above 100 mm Hg without CPR by 4n. ABGs and blood glucose were checked at 5-7 min, 30 min, h, 4 h, and 8 h post-resuscitation. MAP was maintained tween 90-140 mm Hg with normal saline, trimethaphan (TMP), d dopamine (D) or norepinephrine (NE) as needed. Beginning 5 min post-resuscitation, cats received in an unblinded, random thion either N 10 μ g/kg over 2 min plus 2 μ g/kg/min for 8 h or nilar volumes of the N diluent (placebo [P]). The N diluent nsists of a mixture of ethanol and polyethylene glycol 400 asoplied by Miles Laboratories. Following return of continuous

EEG activity (1-2 h) morphine 0.1 mg/kg and either diazepam 0.2 $\,$ mg/kg or midazolam 0.5 mg/kg were administered iv for sedation.

Statistical differences between N and P cats were determined by use of unpaired t tests. Intragroup differences were determined with ANOVA, followed by paired t tests with corrections for multiple comparisons. A probability of < 0.05 was considered significant. All data are reported as mean ± SD.

Results: One cat was excluded from data analysis for failure to be resuscitated within 4 min. There were no significant differences in MAP, CVP, or HR between N or P groups except for a greater MAP in the N cats at CONT, a lower HR and CVP in the N cats at 30 min and 1 h, respectively (Table). MAP was decreased in the N cats at 30 min, 1, 4, and 8 h compared to CONT values. MAP in the P cats was decreased at 30 min and 8 h when compared to CONT values. There were no significant differences in ABGs between N and P treated cats at anytime. Blood glucose was significantly greater in N cats at 1, 4, and 8 h compared to P cats.

Four of six P cats required treatment with TMP (6.1±6.7 μg/kg) to maintain MAP below 140 mm Hg. All N cats required either D (300±145 μg/kg) or NE (829±770 μg/kg) to maintain MAP above 90 mm Hg. (Total doses over 8 h).

Discussion: If calcium entry blockers such as N are to have a role in the treatment of patients successfully resuscitated from cardiac arrest, then N must be shown 1) to have beneficial effects upon the brain, and 2) to have no deleterious systemic or hemodynamic effects. Previous studies have shown that N can attenuate neurologic damage following non-cardiac arrest complete cerebral ischemia (1,2). In the current study we have shown that N, in large doses, can be administered to cats following successful resuscitation from cardiac arrest, with vasopressor support. In pilot dose-seeking studies, we found that doses of N larger than 10 μg/kg + 2 μg/kg/min were associated with unacceptable hypotension and acidosis. The etiology and significance of the elevation of blood glucose observed in the N cats is unclear and requires further examination.

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				Table			
		CONT	<u>5-7 MIN</u>	30 MIN	<u>1 H</u>	<u>4 H</u>	<u>8 H</u>
<u>MAP</u>	P	138±16	112±35	100±8#	108±21	101±24	102±18#
	N	156±11*	131±32	92±11#	101±16#	108±17#	95±15#
<u>HR</u>	P	205±17	251±31	264±29	242±25	222±33	206±41
	N	233±32	234±5	227±14*	220±23	228±16	196±7
<u>CVP</u>	P	5.0±2.6	8.7±2.2	6.0±2.4	6.3±1.6	4.7±1.4	3.4±1.1
	N	2.0±3.2	8.6±4.5	4.0±2.9	2.7±2.7*	3.0±1.8	3.0±2.3
GLU	P	112±34	393±203		223±149	175±79	179±49#
	N	119±36	581±186		367±118#*	288±32*	277±36*

P = Placebo (n = 6)N = Nimodipine (n = 8) GLU = Blood glucose * p< 0.05 P vs. N # p< 0.05 vs. control

Title: CHANGES IN ALPHA 1 ACID GLYCOPROTEIN DURING LABOR

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Introduction an acute phase plasma protein which increases in response to stress (1). It is also the main binding protein for certain basic drugs such as lidocaine, bupivacaine and meperidine (2). Because these drugs are commonly used in parturients any change in AAG either during or immediately following labor may affect the active fraction of these drugs. To date we have no information on changes in AAG concentration during labor and for that reason this study was undertaken.

Methods Only healthy women, at term, were included in the study. All were due to have induction of labor by artificial rupture of membranes. Patients with pre-eclampsia and those on concommitant medication were excluded from the study. Patient and local University Medical Research Ethical Committee approval was obtained. Ten millilitres of venous blood was obtained before labor, during early labor, established labor, at delivery and day 1 post partum. The samples were centrifuged and the supernutant serum was stored at -20°C until analysis. AAG estimations were by Beckman Array Protein analysis using a rate methylometer. Statistical analysis was by students paired 't' test.

Results Thirty one patients were included in the study. Ten received epidural analgesia for pain relief and twenty-one received narcotic analgesia. Duration of labor and parity were similar in both groups. Figure 1 shows mean serum AAG levels (SEM) during the various stages of labor. Patients receiving narcotics had a significant increase in levels during labor from 0.41 gl^{-1} before labor to 0.47 gl^{-1} at delivery (p < 0.001) while patients receiving epidurals had no rise in levels during labor. This rise was not related to the duration of labor. Both groups had significantly higher levels on day 1 post partum rising from 0.41 to $0.60~\mathrm{g1}^{-1}$ (p < 0.001) in the narcotic group and from 0.41 to 0.57 gl^{-1} (p < 0.02) in the epidural group. AAG concentrations in cord blood were 0.19 and 0.17 gl-1 respectively.

<u>Discussion</u> AAG rises in patients undergoing surgery about 6 hr following skin incision, reaching a peak at 48 hr and does not begin to decline until about 120 hr (3). There appears to be no difference in trend between major or minor surgery. Because AAG is the main binding protein of many drugs used in obstetric practice the active (unbound) fraction of these drugs will be inversely proportional to the serum concentration of this protein.

This study would suggest that as the AAG concentration increases during labor the efficacy, distribution, placental tranfer and clearance of these drugs may be altered. Epidural analgesia, on the other hand, ablates the stress response and no rise in AAG is seen while the block is effective.

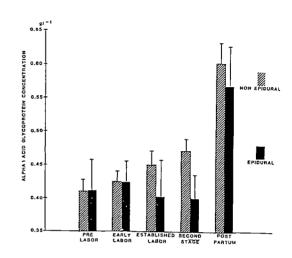


Figure 1. Mean serum levels of AAG (SEM).

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Title:

COMPARISON OF INTRAPLETRAL BUPIVACAINE VERSUS INTRAMUSCULAR NARCOTIC

FOR TREATMENT OF SUBCOSTAL INCISIONAL PAIN.

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INTRODUCTION. Several studies have demonstrated the efficacy of administering local anesthetic via an intrapleural catheter in controlling post-operative pain from subcostal incisions (1,2,3,4). The vast majority of patients studied required no additional pain medication other than intrapleural bupivacaine. The intent of this study was to evaluate the effect of intrapleural bupivacaine given every six hours on the post-operative hospital course and to determine the time course of pain relef from a single bolus of intrapleural bupivacaine. An analysis of patients randomized to a group receiving intramuscular narcotic injections or intrapleural bupivacaine was conducted. Narcotic requirement, pulmonary function, pain control over 24 hours were studied. In addition, length of recovery room and hosp tal stay were evaluated.

METHODS. Eighteen adult patients undergoing cholecystectomy were consented and enrolled in this study which was approved by our Human Subjects Committee. Those patients randomized to the catheter group had an intrapleural catheter placed percutaneously through the six or seventh intercostal space as previously described (5). The catheter was directed medially and cephalad 6 cm. The position was determined by chest x-ray. In both the IM and catheter groups, narcotics were ordered on a prn basis. Patients were told to request narcotics for pain.

Up to 3 mg/kg (20 to 30 mls) of 0.5% bupivacaine with 1:200,000 epinephrine were injected every six hours over a twenty-four hour period. Sensory anesthesia to pinprick was obtained over the thorax unilaterally in all cases.

Pain was assessed using the visual analog scale(VAS) six hours after each bolus. At that time, patients were asked to indicate their average level of pain over the previous six hours. Measurements of their oxygen saturation and forced vital capacity (FVC) were taken twenty-four hours following the operation. The FVC is reported as percent of the preoperative value. Cumulative 24 hour narcotic requirement con post-operative day one is reported in morphine equivalents.

In addition to the above measurements, the time course of analgesia from a single bolus of bupivacaine was studied. The fourth bolus was chosen so that the effect of residual operative anesthesia would be minimized. Visual analog scores were recorded immediatly prior to and at hourly intervals following the bolus. FVC and oxygen saturation were recorded prior to and at 1 and 6 hours following the bolus. All data were analyzed for statistical significance by either the two tailed, unpaired Student's t-Test or the Chi-Square test.

RESULTS. There was no statistical difference in subject age, distribution of sex, or preoperative pulmonary function (tables. Even though the IM group received significantly more narcotic intraoperatively, 88% of the patients in this group required additional narcotic in the recovery room compared to 33% in the catheter group (p<.01). Patients receiving intrapleural bupivacaine had significantly better post-op analgesia over the first 24 hours when compared with the IM group (mean VAS 4.3 vs 3.2). Despite these findings, there was no difference in the narcotic requirement over this same 24 hour period. There was also no difference detected between groups when comparing pulmonary function tests at 24 hours post-op, recovery room

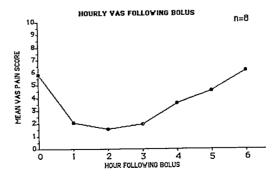
stay, or time to discharge (table). No difference in time to first ambulation between groups was found (not shown).

The duration of a single bolus was analyzed in closer detail. Hourly VAS scores following the last bolus were significantly decreasec from 5.9 to 2.1, a difference which persisted until the fourth hour (p<.01) see graph. This correlates well with the mean time for requesting additional narcotic (4hrs,2mins±1hr,16mins). A significant improvement in FVC from 1.2±0.5 liters to 2.0±0.7 liters was detected an hour after the last bolus(p<.01). However, no statistically significant improvement could be demonstrated six hours after the last bolus (1.5±0.8 liters). No difference in oxygen saturation was found during that same interval.

Small, asymptomatic pneumothoraces (1to5%) were detected following three of the nine catheter placements but all had resolvad spontaneously by the next morning.

DISCUSSION. Bolus intrapleural bupivacaine is effective in providing short term post-operative analgesia for a period of approx. 4hrs. Pulmonary function can be improved but showed no improvement by six hours post injection. There were no differences in post-op narcotic requirement, recovery room time, hospital stay, or time to ambulation in patients treated with either IM narcotics or intrapleural bupivacaine. Future studies are suggested to determine the optimal regimen for administration of local anesthetic in the intrapleural space.

	IM		CATHETER
N	9		9
MEAN AGE (yrs)	45		38
SEX	2M; 7F		2M; 7F
PREOP FVC (liters)	3.0_0.8		3.4_1.1
PREOP 02 SAT (%)	96_1		96_1
OPERATING ROOM NARC. (mg)	26_12	1	16_14
RECOVERY ROOM NARC. (mg)	9_6	•	4_8
POST-OP DAY 1 NARC. (mg)	31_1		25_17
NO. INJ. FOR 24HRS PER PATIENT	3.2_1.3		3.8_1.4
PERCENT PREOP. FVC	41_0.9		46_23
02 SAT (%)	93_2		95_4
VAS (2-10)	4.8_2.9	•	3.2_1.6
RECOVERY ROOM TIME (min)	126_27		139_56
TOTAL HOSPITAL STAY (days)	4.0_0.9		4.0_0.8
SIGNIFICANCE: * p<	.05 ! p< .01		



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Title: Effects of Beta-Adrenergic Blockade on Serum Potassium Following Succinylcholine

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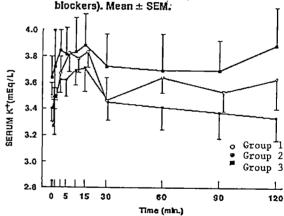
Introduction. There is increasing evidence to suggest β_2 adrenergic stimulation promoting the entry of potassium (K+) into cell, may have an important influence on potassium hemostasis (1,2). Animal studies have shown cardioselective and nonselective adrenoreceptor blocking drugs augment and prolong release of K+ following succinylcholine (SCh) (3,4). This study examined the changes in serum K+ following SCh in patients receiving beta blocking drugs compared to those receiving no adrenoreceptor blocking drugs.

Twenty-four adult patients scheduled to undergo retinal reattachment and/or vitrectomy were studied after informed consent. The patients were divided into three groups of eight patients according to the blocking medications they were receiving. Group 1, the control, received no beta-blockers. Group 2 received cardioselective beta-blockers (atenolol and metoprolol). Group 3 received nonselective beta-blockers (timolol, and propranolol). Patients -1 were premedicated with morphine $0.1_{\overline{1}}0.2$ mg kg $^{-1}$ and scopalamine $0.02_{\overline{1}}0.03$ mg kg $^{-1}$ i.m. 45 to 60 minutes prior to induction of anesthesia. Anesthesia was induced in each patient with thiopental 4-5 mg kg and maintained with 60% nitrous oxide in oxygen and 1% inspired isoflurane. Once a steady state of anesthesia was achieved SCh 1 mg kg was administered i.v. ater by endotracheal one minute later intubation. Heart rate (HR) and mean arterial blood pressure (MAP) were continuously monitored by continuous EKG and automatic oscillometer, respectively. The patients were ventilated during the induction and maintenance of anesthesia to maintain ETCO (35+5 mm Hg). Normal saline was infused in all patients for maintenance of fluid Blood samples were collected from an antecubital vein immediately after placement of a cancula, after induction of anesthesia but before Sch and at 1, 3, 5, 10, 15, 30, 60, 90 and 120 minutes following SCh. Serum K+ was analyzed by direct potentiometry. Change in serum K+ from control within each group was analyzed using analysis of variance (ANOVA) and Dunnett's test. Comparisons among groups was done by ANOVA. P<0.05 considered significant.

Results. The serum K+ prior to and following SCh are shown in Figure 1. There was no significant difference in serum K+ prior to SCh between the groups. Increase in serum K+ was seen at 3 minutes with the peak at 15 minutes following SCh in all groups. There was no significant difference in rise and over the time course observed in serum K+ among the three groups. The percent change in HR and MAP three minutes following larny30scopy was 22.2%, 8.4%, 21.2% and 5.6%, -11.4%, 10.6%, in Groups 1, 2 and 3, respectively. The HR increased significantly in Group 1 (P=0.035). There was no significant difference in MAP.

In this study, the increase in serum Discussion. following SCh may have been attenuated in the presence of membrane stabilizers, thiopental and inhalation anesthetics (5). Additionally, sampling from venous blood may have affected K+ levels seen. It is possible that no exaggerated or prolonged response to K+ was seen due to decreased efflux in these small groups of patients studied. Maryniak et al (3) found that there is no short term (6 minute) change in time course of serum K+ following Sch. Our data confirms their impression over a longer (120 minute) time period. studies where greater efflux in serum K+ following SCh may be necessary to evaluate effect of adrenoreceptor blockade on potassium hemostasis.

Figure 1: Serum potassium changes from pre-induction levels in Group 1 (no beta-blockers), Group 2 (cardioselective), Group 3 (nonselective beta-



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Ventilatory Frequency Does Influence Emuracy of ETCO, Measurements: Analysis of Five Capnometers Title:

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Introduction. An accurate high-frequency response is mandatory when end-tidal carbon dioxide (ETCO2) is monitored during pediatric general anesthesia. Is monitored during pediatric general anesthesia. The possibility that as frequency of ventilation increases the accuracy of ETCO values decreases has been investigated for different configurations of sampling (1,2), but not for different CO₂ analyzers. The aim of this study was to compare the accuracy of ETCO₂ measurements at increasing frequency of five commonly used cappometers available at our commonly used capnometers available at our hospital.

Capnometers studied were Datascope Methods. Hewlett-Packard (47210A Capnometer), (Accucap). Narkomed 3 (Capnomed), Puritan-Bennett (Datex CO Monitor), and a Perkin-Elmer multiplexed mass spectrometer (MGA 1100). All machines were allowed the warm-up period suggested by their manufacturers and were then calibrated if possible. Some had no external calibration adjustment. Sampling ports of the five capnometers were all placed next to a common sampling point with a continuous outflow of 6 1/min. Changes in CO₂ concentration were generated by a solenoid valve (Humphrey 062E1) driven from 8 to 101 cycles per minute, switching between 100% oxygen (O₂) and O₂ with 6.94% CO₂ (Barometric pressure 737 mm Hg, CO₂ 51.4 mm Hg) (3). Frequencies were chosen to simulate a range that might be used for children during general endotracheal anesthesia. At every rate the displayed value of ETCO₂ was recorded. Also recorded, when available, were the displayed values for frequency and inspired CO2.

Results. The data from each capnometer studied are shown in Table 1. The error is reported as the observed value minus the true value (51.4 mm Hg). All capnometers under reported ETCO2 frequencies above 31. The mass spectrometer had the most error, presumably because of its long sampling catheter length. The Hewlett-Packard had the least error, presumably because it has no sampling catheter, but has an in-line analysis chamber. Those machines that determine ventilatory rate (Datascope, Hewlett-Packard and Perkin-Elmer) did so with an accuracy of ± 1/min of the actual rate. The indicated inspired CO₂ ranged from 0 to 28 mm Hg.

Discussion. It is possible for the respiratory rate of a child under halothane anesthesia to exceed 60/min and therefore generate gasconcentration changes of twice that frequency (3).

Our data indicate that capnometers consistently underestimate the patient's end tidal at high frequency. concentration Therefore. display of ETCO must be used only as an aid in adjustment of minute ventilation to clinically acceptable limits, otherwise the anesthesia provider might adjust ventilation in the opposite direction to that needed for patient safety. The genesis of the errors is thought to be mixing of adjacent breaths both during transport down the sampling catheters and in the analysis chambers.

1. Capnometers using Conclusions. catheters do not give accurate values for ETCO₂ at high frequencies. 2. The anesthesia provider must be aware of this limitation when using these monitoring devices.

Results * of ${\rm ETCO}_2$ measurements at frequencies reported by five Table 1. different capnometers.

Frequency R/min		etco ₂						
	Data- scope	H/P	Narkomed 3	P-E	P/B			
8	+6.6	+1.6	+2.6	-2.4	-1.4			
16	+5.6	+1.6	+1.6	-2.4	-1.4			
31	+3.6	+0.6	+1.6	-3.4	-1.4			
53	-0.4	-0.6	-0.6	-4.4	-2.4			
72	-3.4	-0.6	-1.4	-6.4	-3.4			
84	-5.4	-0.4	-1.4	-8.4	-5.4			
101	-7.4	-1.4	-3.4	-11.4	-7.4			

* Reported as + observed values from known ETCO, (51.4 mm Hg).

Datascope = Datascope (Accucap)

= Hewlett-Packard (47210A Capnometer)

Narkomed 3 = Narkomed 3 (Capnomed)

= Perkin-Elmer Multiplexed Mass P-E

Spectrometer (MGA 1100)

= Puritan-Bennett (Datex CO, Monitor)

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Title: MIDAZOLAM ALTERS MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS

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Introduction. Somatosensory evoked potentials (SSEPs) are a common monitor of neural function during cental nervous system surgery. Physiologic variables, surgical factors, technical problems and anesthetic agents can all affect the amplitude and latency of the waveforms obtained. A narotic based aresthetic is often used during monitoring, however, an amnestic agent is desirable to prevent awareness. This study was designed to measure the alteration in the median nerve SSEP with an induction-infusion regime utilizing midazolam (0.2 mg/kg induction bolus and 5 mg/hr infusion).

Methods. Ten ASA I and II patients ages 21 to 64 and having lumbar spinal surgery were included in this institutionally approved study. Unpremedicated patients had their fluid deficits replaced and disc electrodes placed with collodion at F_2 , C_4 ' (International 10-20 system) and over the second cervical vertebra. A bar electrode stimulated the left median nerve at the wrist at 8.7 Hertz with 300 microseconds constant current pulses at 2 milliamp above motor threshold. A Nicolet CA 1000® machine filtered (5-250 Hertz) and averaged the responses (250 per waveform). Duplicate baseline recordings were obtained, and midazolam (0.2 mg/kg) was given over 50 seconds followed by an infusion of midazolam 5 mg per hour. Pancuronium up to 0.12 mg/kg was given as needed, ventilation was assisted to maintain pCO2 between 35-45 torr, and heart rate, blood pressure and SSEPs were recorded at 1 minute intervals for ten minutes post induction. The cervical response (15 msec), and the cortical P_1 (17 msec), N_1 (20 msec) and P_2 (26 msec) were analyzed for latency, amplitude (P_2 minus N_1) and central conduction time (CCT) charges. The Friedman twoway analysis of variance was used to compare results

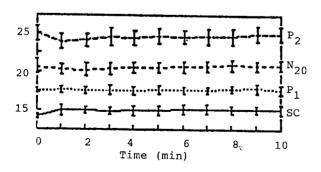


Figure 1. Average latency (\pm SEM) following induction for cervical SC, cortical P $_1$, cortical N $_{20}$ and cortical P $_2$ values.

at 0 through 10 minutes and a signed ranks test was used to confirm significant differences. After the study period, the patients were given scopolamine 0.4 mg intravenously and sufentanil titrated to their anesthetic needs as the surgical procedure was then conducted.

Results. Figure 1 shows the average absolute latency results of the cervical P_1 , and cortical P_1 , N_1 and P_2 . Increases in cervical and cortical $(N_{20},\,P_2)$ latencies were statistically significant $(p \leq 0.05)$, however the absolute latency charges were small. The average cortical amplitude, shown in Fig. 2, decreased to 50% of baseline. This amplitude reduction was statistically significant at 5 minutes from baseline. All waveforms were easily obtainable throughout the study and heart rate and blood pressure were stable.

Discussion. This study demonstrates that significant but small charges in the latercy values occurred in addition to a significant reduction in cortical amplitude. This decrease in amplitude was maximal at 5 minutes following which it stabilized. This rapid charge is consistent with the rapid onset and action of this drug. This rapid action and stabilization coupled with the minimal charges in latercy may make it a good induction agent. The fact that these patients were all monitored successfully using posterior-tibial nerve SSEP suggests it may be an adequate anesthetic technique for monitoring. The decrease in amplitude, however, may make it an undesirable drug in patients whose preinduction amplitudes are small.

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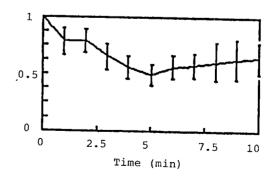


Figure 2. Normalized amplitude (\pm SEM) following induction.

Title:

REPRODUCTIVE AND TERATOGENIC EFFECTS OF SUFENTANIL AND ALFENTANIL IN SPRAGUE-DAWLEY RATS

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Introduction. For the past ten years we have studied the reproductive and teratogenic effects of the inhaled anesthetics in several rodent models. However, until recently, reliable studies with th∋ parenteral anesthetic agents and narcotics have mot been possible because of the extensive matermal toxicity associated with bolus administration of even relatively low doses of these drugs. The use of chronically implanted s.c. osmotic minipumps has facilitated delivery of high total doses of local anesthetics and narcotics at a constant rate. throughout organogenesis, without causing adverse maternal physiologic effects. In the present study we tested the reproductive and teratogenic effects of sufentanil and alfentanil using this method of drug delivery.

Methods. Two separate experiments of similat design were performed using a total of 168 time1pregnant rats. In each experiment, on day 5 of pregnancy, an Alzet, model 2ML2, osmotic minipump with & 15-day drug supply was implanted s.c. on the back of each rat under general anesthesia. In the first ezperiment, 128 rats were divided into four groups amc treated with either: 1) saline (control), (n-39); 2; a low dose of sufentanil, 10 ug/ kg/day (n-30); 5; an intermediate dose of sufentanil, 50 ug/kg/day (== 30); or 4) a high dose of sufentanil, 100 ug/kg/dz3 (n=29). In the second experiment, 40 rats were divided into two groups and treated with either: saline (control), (n=20); or 2) a high dose of a fentanil, 8 mg/kg/day (n=20). Dosages of the narcotics were based on data from preliminary studies in which we determined the highest dose which dic not cause maternal weight loss; respiratory depression always occurred at a higher dose than weight loss. On day 20 of pregnancy, rats were killed by CO2 inhalation and cesarean section was performec. The uterus was examined and the number and position of live and dead fetuses, resorptions, and implantations were recorded. The weight and sex of each live fetus were determined and all were examined for external abnormalities. Subsequently, every other fetus was examined with a dissecting microscope either for visceral or skeletal abnormalities. All examinations were done without knowledge of the treatment group. The percentage of abnormal fetuses in each litter of each treatment group was computed and group means were compared with control group means by one way analysis of variance (ANOVA). Student's t test was used as an a posteriori test when differences were found with ANOVA. p < 0.05 was considered significant.

Results. No rats treated with sufentanil died during the experiment. Four rats treated with alfentanil died in the first four days after pump implantation. Otherwise, no adverse effects were observed during the experiments. There were no differences in weight gain among any of the groups in either experiment. There were no significant differences among the groups in pregnancy rate, number of implantations and live fetuses, percent fetal wastage, and mean fetal weight. There were more femals offspring in the alfentanil group than in their control group, although this difference was probably due to a lower than usual percentage of male offspring in the control group. A total of 1174 off-spring were examined; there were no significant teratologic findings observed in any group.

In the present study, we found <u>Discussion</u>. both sufentanil and alfentanil to be devoid of adverse reproductive and teratogenic effects. These results are similar to those reported with the parent compound in this series, fentanyl (1). However, our results differ from those of studies of the older narcotics, morphine, meperidine and methadone, in which adverse reproductive effects were reported with high doses (2-4). In all of these investigations, narcotics were given by bolus injection. From the doses and maternal side effects reported in these studies, and from our own studies, we surmise that the test animals experienced significant respiratory depression. Thus, it is not appropriate to compare the results of the present study with those of past studies as their design was flawed. We conclude that sufentanil and alfentanil do not cause adverse reproductive effects in Sprague-Dawley rats when administered throughout organogenesis with chronically implanted osmotic minipumps. These pumps are of great value in reproduction and teratology studies as they: 1) permit large doses of drugs to be administered before maternal side effects occur; 2) reduce the need for other potentially confounding interventions, such as repeated handling and injection of pregnant animals; and 3) avoid the possibility of causing narcotic withdrawal effects between doses.

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C		Sufent	(ug/kg	/day)		Alfent 8 (mg/
Summary of Reproductive Indices and Fetal Exam.	Cont	10	50	100	Cont	kg/day
No. of rats studied	39	30	30	29	20	20
No. of pregnant rats	34	25	22	26	18	11
Pregnancy rate (%)	87	83	73	90	90	69
Starting dam weight (g)	202	202	203	201	204	207
Weight at C-section (g)	342	347	332	327	359	345
No. of implantations/rat	11.9	12.0	12.0	11.5	11.7	11.3
No. of live fetuses/rat	11.6	11.8	11.4	10.7	11.2	9.8
Percent resorptions/rat (%)	2.5	1.6	5.1	7.1	3.7	11.5
Mean fetal weight (g)	4.5	4.6	4.7	4.7	4.6	4.3
Percent females/rat (%)	49	53	52	49	44	60
External examinations;						
No. of fetuses examined	394	296	227	257	202	108
Any abnormalities (%)	0.0	0.0	0.0	0.0 ·	0.0	0.0
Runt (%)	0.2	0.4	0.0	0.3	0.6	3.5
Visceral examinations:						
No, of fetuses examined	198	148	112	130	100	53
Major malformations (%)	0.0	0.0	0.0	0.0	0.0	0.0
Minor anomalies (%)	7.9	2.2	5.0	3.9	5.2	3.1
Skeletal examinations:						
No. of fetuses examined	196	148	115	127	102	55
Major malformations (%)	0.0	0.0	0.0	0.0	0.0	
Minor anomalies (%)	0.0	1.1	0.0	0.0	0.9	
Develop, variants (%)	25.5	34.0	32.3	30.5	16.8	33.9

Title: VECURONIUM INHIBITS HISTAMINE N-METHYL TRANSFERASE

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Introduction. Vecuronium (VEC) has minimal cardiovascular effects and causes no histamine (HA) release. Several compounds can inhibit histamine N-methyl-transferase (HNMT) in vitro. Inhibition of this primary metabolic enzyme could cause potential interaction with drugs which liberate HA. We performed kinetic studies using VEC and purified HNMT, and examined the plasma from patients to determine whether VEC in clinically used concentrations could inhibit HNMT.

Methods. HNMT was prepared according to Bowsher et al. (1). All chemicals were of reagent grade. Pure VEC was supplied by Organor. In the kinetic studies, HNMT was diluted 1:1000 and the reaction velocity measured at 10⁻⁸ to 10⁻³ M VEC, with [HA] 1 to 100 μM and S-adenosylmethionine (SAM) 0.5 to 4 μM. In clinical studies, 19 elective surgical patients from whom informed consent was obtained were anesthetized with N2O/Halothane/O2 and intubated without relaxants. Ventilation was contolled (pCO₂= 40±3 torr) and end-tidal halothane was maintained at 0.7 %. Subjects were randomly assigned to receive 0.1 mg/kg (group 1; N=10) or 0.2 mg/kg (group 2; N=9) VEC. Arterial plasma samples were harvested both before and 2 minutes after the administration of VEC. HA levels were measured in duplicate with duplicate internal standards using a sensitive radioenzymatic assay. The assays were performed blinded to the original design. Data were analyzed by paired and unpaired t-tests.

Results. Our enzymatic studies indicated that VEC inhibits HNMT; apparent K_i =1 μ M (fig. 1). The inhibition obeys the equation:

$$1 / V = (K_m / V_{max}) (1+[I] / K_i) (1 / [S]) + 1 / V_{max}$$

where V is the rate, V_{max} the highest rate at a concentration of VEC, [I] the concentration of VEC, K; the inhibitor constant, K_m the Michaelis constant, and [S] the SAM concentraion and

$$\begin{array}{l} 1/V = (K_m / V_{max}) (1 + [I] / K_i) (1 / [S]) + \\ (1 / V_{max}) (1 + [I] / K_i) \end{array}$$

where [S] is the HA concentration. Lineweaver-Burk plots demonstrate that inhibition is competitive with respect to SAM (K_i =1.4 μ M) (fig. 2) and noncompetitive with respect to HA $(K_i=1.2 \mu M)$ (2).

Although the efficiency of the HNMT enzyme decreased from 87.7 ± 24.6 cpm/pg HA to 72.7 ± 18.2 (p ≤ 0.025) in group 1 and decreased from 97.9 ± 21.3 to 58.4 ± 14.7 (p ≤ 0.0005) in group 2, patients who received VEC had no significant in group 2. significant increase in HA levels. There were no statistical differences between the samples obtained prior to VEC administration but group 1 vs. group 2 post-VEC differed significantly $(p \le 0.05)$.

Discussion. While VEC inhibits HNMT, there are few reports of significant hypotension with its administration. HNMT is the major, but not exclusive, catabolic enzyme for HA in humans (3). Our data demonstrate that VEC inhibits HNMT in clinically used concentrations. Thus, doses of VEC ≥ 0.1 mg/kg may cause a decrease in the metabolism of HA, accentuating or prolonging the hypotensive action of concurrently administered HA liberating drugs.

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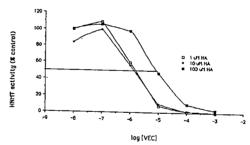


Fig. 1. Inhibition of HNMT by VEC. Activity vs. log[VEC]. Curves shown are for 1, 10, and 100 μM. Solid lines are interpolations of average values.

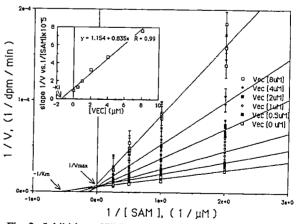


Fig. 2. Inhibition of HNMT by VEC. 1/V vs. 1/ [SAM]. Inset: Slope of main plots vs. [VEC]. All curve fits are linear regressions. Bars represent SE of the data.

Title:

HALOTHANE ANTAGONIZES DIGITALIS TOXITIY IN CANINE PURKINJE FIBERS

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Introduction. Cardiac glycosides inhibit Na+, K+-ATPase activity. The resultant cytoplasmic accumulation of Na+ augments Na⁺-Ca²⁺ exchange and raises intracellular ${\tt Ca^{2+}}$ which activates the "transient inward" current $({\tt I_{TI}})^{.1}$ The cellular correlate of \mathbf{I}_{TI} activation is the delayed after depolarization (DAD), a membrane potential oscillation occurring after repolarization1 (see figure). DAD's can trigger action potentials and initiate sustained dysrhythmias. 1

Halothane shifts the dose response curve to the right with respect to doses of cardiac glycosides producing dysrhythmia and/or death.2

The goal of this study was to determine the electrophysiologic mechanism by which halothane diminishes digitalis toxicity.

Methods. Dogs were anesthetized with pentobarbital 30 mg.kg-1 I.V.; the heart was rapidly removed and placed in cold, oxygenated (95% 02/5% CO2) Krebs Henseleit (K-H) buffer containing 121.4 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 1.2 mM MgSO4, 21.9 mM NaHCO3, 1.2 mM KH2PO4, 11.1 mM glucose. Furkinje fibers were excised, placed in a tissue bath and superfused with 37°C K-H buffer. Intracellular action potentials were recorded using 3M KCl filled microelectrodes. DAD's were induced by 30-40 min of superfusion with 2 x 10^{-7} M ouabain, 3 and the amplitude (AMP) and coupling interval (CI) of DAD's measured after 19-beat trains of pacing (1 msec duration, 2x threshold) at paced cycle lengths (CL) from 200-1000 msec. Halothane 0.5%, 1% and 2% was added to aerating gas using a calibrated vaporizer. and the effects of halothane on DAD AMP and CI determined. The effect of increasing extracellular Ca2+ on DAD's in the presence of halothane was examined by doubling the superfusate Ca concentration from 2.5 to 5 mM in the presence or absence of 2% halothane and measuring the effects on DAD's. One or two way ANOVA and Bonferroni's t-test were used to analyze data. A p<0.05 was considered significant.

Results. Ouabain superfusion produced typical DAD's with AMP's that increased and CI's that decreased as paced CL decreased. As expected, at paced CL's less than 500 msec, secondary DAD's of increased AMP and CI appeared. Ten studies confirmed prior results3 that the ouabain toxic preparations are stable for at least one hour with constant values of maximum diastolic potential, DAD AMP and DAD CI.

In 8 preparations, increasing halothane concentrations produced dose related decreases in DAD AMP (p<.05) without significantly changing DAD CI. At a paced CL of 400 msec, for example, DAD AMP was decreased by 20% by halothane 0.5%, 22% by halothane 1% and 35% by halothane 2%.

In 8 experiments, doubling extracellular Ca to SmM during administration of halothane 2% increased DAD AMP towards control values at each paced CL. Ata CL of 400 msec, halothane 2% decreased DAD AMP by 12% in 2.5 mM Ca but by only 12% in a buffer Ca of

5mM. Doubling buffer Ca in the absence of halothane increased DAD AMP by 30%.

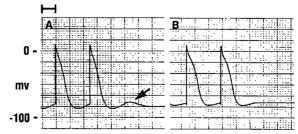
In several preparations, sustained dysrhythmias were triggered by pacing. When halothane was administered, the dysrhythmia rapidly terminated and could not be reinduced until several minutes after halothane administration ceased.

Discussion. In cardiac tissue, halothane reduces the influx of calcium during the cardiac action potential4 and alters release of intracellular calcium stored in sarcoplasmic reticulum. 5 Both of these sources of calcium are considered important in the generation of I_{TI} and, therefore, in DAD generation and digitalis toxic dysrhythmias. 1 The results of the present study suggest that halothane reduces digitalis toxicity primarily by decreasing DAD amplitude. Competitive inhibition of calcium entering into the cardiomyocyte, suggested by the DAD response to increased extracellular Ca²⁺ in the presence of halothane, is a likely mechanism for the effect of halothane.

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200 msec



Legend. Transmembrane action potential recordings from a single ouabain toxic Purkinje fiber before (A) and after (B) administration of halothane 0.5%. Time and amplitude calibrations are shown and the arrow identifies the DAD. Halothane reduced the amplitude of the DAD. Paced cycle length=500 msec.

Title : ASPIRATION PNEUMONIA PROPHYLAXIS - USE OF ORAL EFFERVESCENT CIMETIDINE IN OBSTETRIC ANESTHESIA

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Introduction. Pulmonary aspiration of acid gastric contents remains a major hazard for obstetric patients undergoing general anesthesia because in these patients the presence of a high gastric content volume or a low gastric pH cannot be excluded (1). Routine antacid prophylaxis is established practice in obstetric anesthesia. Oral cimetidine given one to three hours prior to surgery, i.e. not in emergency circumstances, is effective in reducing the acidity and the volume of gastric contents (2). Sodium citrate given just prior to induction in emergency anesthesia is effective most of the time in decreasing gastric acidity but is associated with a large mean volume of aspirate (3). This study was undertaken to assess the effectiveness of a new formulation* combining 800 mg of cimetidine with 1.8 g of sodium citrate, in raising the gastric pH of patients undergoing elective and emergency Cesarean sections.

Methods. The study was approved by the local Ethical Committee and informed consent was obtained from all patients. Twenty three ASA Class I or II patients undergoing elective (twelve) or emergency (eleven) Cesarean section were studied. Elective surgery was done because of previous Cesarean section, breech presentation or cephalopelvic disproportion. Emergency Cesarean section was undertaken for such conditions as fetal distress. preeclampsia, dystocia or unsuccessful trial of labor. Twelve hours prior to surgery no medication was given to patients scheduled for elective Cesarean section. Patients undergoing emergency Cesarean section received various drugs prior to surgery such as betamimetics, betablockers, hydralazine, clcnidine, dipyramidole, meperidine and oxytocine.

Just prior to entering the operating room, half of a tablet of effervescent cimetidine was given with 30 ml of water. Anesthesia was induced with thiopental 5 mg/Kg and tracheal intubation was accomplished with succinylcholine 1.5 mg/Kg. A number 16 nascgastric tube was inserted orally to the stomach immediately after intubation had been completed. All available gastric contents were aspirated. Anesthesia was continued with vecuronium bromide 0.7 mg/kg and, after the birth of the baby, with fentanyl, M20. Proper uterine tone was obtained with an oxytocir infusion. Just before extubation. a gastric content sample was obtained through a fresh nasogastric tube. All pH values were measured with a Beckman 71 pH meter. The average time between effervescent cimetidine intakeand extubation was seventy minutes, with extremes of forty and ninety five minutes.

Results. pH values are shown in table 1. In all patients but one, pH after intubation and prior to extubation were always above 3.5. In the one remaining patient scheduled for elective Cesarean section, gastric pH stayed above 2.5.

Discussion. This study shows that the effervescent formulation combining cimetidine and sodium citrate is effective in raising gastric pH above the critical level of 2.5 when given just prior to obstetric surgery in elective as well as in emergency circumstances. Effervescent cimetidine is an original combination which has an immediate antacid action due to the sodium citrate contained in its excipient. The acid neutralizing capacity of one tablet is 14.8 m Eq H^{+} . The action of sodium citrate is then followed by the gastric acid secretion inhibitory action of cimetidine. This preliminary study shows that the new oral combination, i.e. effervescent cimetidine, is useful in preventing aspiration pneumonia in elective but especially emergency Cesarean section done under general anesthesia.

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INTUBATION	EXTUBATION	INTUBATION	EXTUBATION
4.21	3.82	6.61	6.11
6.73	7.02	6.65	7.54
4.37	3.87	6.82	6.40
7.35	7.00	6.27	6.56
5.84	6.28	5.43	5.72
6.61	6.60	6.30	6.09
6.00	3.89	6.32	5.74
6.21	7.04	5.45	5.40
6.10	6.15	4.50	6.04
4.94	5.87	6.00	6.08
6.83	6.66	3.94	4.51
		3.38	5.02
Emergency Ce	sarean	Elective Ces	arean
sections		sections	

Intragastric pHs of women (twenty three) treated with 400 mg cimetidine + 0.9 g sodium citrate just prior to induction for elective and emergency Cesarean sections.

^{*} Tagamet 800 effervescent - Laboratoires Smith Kline & French

ANESTHETIC AGENTS INFLUENCE THE CEREBIAL BLOOD FLOW RESPONSE TO HYPOXIC HYPOXEMIA

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INTRODUCTION

Hypoxic hypoxemia due to mechanical mishaps and misplaced endotracheal tubes is still the most common cause of intraoperative-brain damage. The cerebral blood flow (CBF) response to hypoxic hypoxemia may be important in determining the onset and extent of the cerebral damage. The influence of anesthetic agents on the CBF response to progressive hypoxemia has not been previously assessed. The aim of this study was to compare and contrast the changes in regional CBF (rCBF) to progressive hypoxic hypoxemia during three anesthetic regimens.

METHODS

The protocol was approved by the Institutional Council on Animal Care. The CBF response to progressive hypoxic hypoxemia was assessed in 16 cats of either sex using the radiolabelled microsphere technique. The animals were divided into three groups to assess the influence of three different anaesthetic regimens; group I - pentobarbital anesthesia (n = 5) group II - isoflurane anesthesia 1% (n = 7) group III - isoflurane anesthesia 2% (n = 4). Following the induction of anesthesia with ketamine, all animals were intubated and mechanically ventilated and end-tidal C02 was maintained between 30 - 35 mmHg. A femoral arterial catheter was inserted for direct measurement of blood pressure and blood sampling. Through a left thoracotomy, a left atrial catheter was inserted for the injection of microspheres. Hypoxic hypoxemia was created by the introduction of nitrogen to the inspired gas mixture. The inspired oxygen concentration was continuously monitored using a polarographic oxygen analyzer. Serial rCBF (ml/100 gm/min) was determined by injection of microspheres labelled with Ce¹⁴¹, Sr85, Sc⁴⁶ or Cr⁵¹. CBF was determined at iour points: Fi0₂ of .21, .15, .11 and .09. Blood gases were withdrawn for determination of arterial p02 and oxygen saturation at each point of CBF determination. Sodium bicarbonate was given when required to keep pH in the normal range. Throughout the experiment the temperature was maintained in the normal range by using a thermal blanket. Inspired and end-tidal isoflurane concentration was monitored with a Puritan-Bennett anesthetic agent monitor. Blood loss during the insertion of the catheters and surgery was replaced with appropriate amounts of Ringer's lactate. Representative brain samples from the parietal areas, thalamus, oons and medulla were taken for the determination of radioactive counts and then converted to CBF using a computer program. Analysis of the data was performed by plotting percentage change n CBF against change in oxygen saturation and the slope computed using linear regression analysis(1). Both the rCBF of each area as well as the flow computed for the combination of all areas were evaluated. Analysis of covariance was used for comparison between the three groups.

RESULTS

There was wide interanimal variation in the response to progressive typoxemia as well as variation between the regions of the brain. For he parietal areas, there was a significant difference between the tobarbital and 2% isoflurane anesthesia (p<.05) (Fig). Similar indings were observed in other areas sampled. Although the esponse appears to be steepest with pentobarbital, statistical significance was not reached in the medulla, pons, thalamus or combination of all areas (p<0.1).

Absolute CBF during normoxic conditions was significantly higher in

the 2% isoflurane group (152 \pm 40) compared to the pentobarbital group. (50 \pm 8) (p<0.02). However, the absolute flows measured during the most hypoxic conditions (Fi0 $_2$.09) were not statistically different between the groups.

DISCUSSION

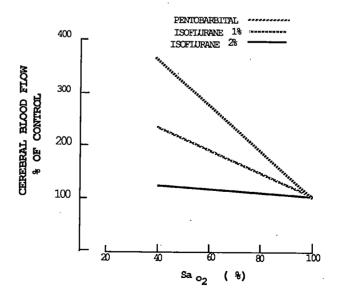
We theorize that the reduction in the response to hypoxemia during isoflurane anesthesia is due to the fact that isoflurane is a potent cerebrovasodilator, resulting in a higher basal blood flow during normoxic conditions, and therefore effecting a smaller increase in flow with the onset of hypoxemia. Although isoflurane anesthesia appears to impair the rCBF response to progressive hypoxemia, the maximum absolute CBF was not affected by the anesthetic regimen.

CONCLUSION

Based on our study, we conclude that anesthetic agents may profoundly influence the rate of CBF increase in response to hypoxic hypoxemia. Two percent isoflurane anesthesia produced near maximal vasodilatation during normoxia with very little further increase during the development of hypoxemia. However, as the absolute maximum blood flow during hypoxemia were not different between the three groups, we concluded there was no significant difference in this defence mechanism against hypoxemia among the three anesthetic regimens studied.

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ESMOLOL FOR THE CONTROL OF HYPERTENSION FOLLOWING NEUROLOGIC SURGERY Title:

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Introduction. Emergence from general anesthesia is frequently complicated by hypertension and tachycardia, particularly in the setting of a neurosurgical or neurovascular procedure. Although usually short-lived, this hyperdynamic state can be severe enough to warrant therapeutic intervention (1). Esmolol hycrochloride (Brevibloc®) is an ultra short-acting ($t_2^{1}=9$ min) cardioselective beta-adrenergic blocking agent which would seem particularly well-suited for this situation (2,3). This double blind, randomized, prospective placebocontrolled study was performed to determine the effectiveness of esmolol vs placebo in treating hypertension in patients emerging from anesthesia following neurosurgical and/or neurovascular surgery.

Methods. After Institutional approval and informed consent, forty patients who exhibited an increase in systolic blood pressure \geq 20% above preoperative levels on emergence from neurosurgical anesthesia were randomized to receive either esmolol (N=21) or placebo (N=19) by continuous infusion via a dedicated intravenous route. Anesthesia was induced with sodium pentothal and following endotracheal intubation, was maintained with N20/02, isoflurane, and $\bar{}$ -entanyl. End-tidal gases were measured via mass spectrometry. Continuous V_5 ECG and direct arterial pressure tracings were recorded. As dictated by the duration of the surgical procedure, isoflurane was discontinued in a timely fashion and the patients were observed for a systolic blood pressure \geq 20% of their preoperative level.

Once this criteria was met, baseline values for heart rate and blood pressure were obtained at one minute before and just prior to beginning of the infusion. Esmolol or placebo was then administered as a continuous infusion to provide a loading dose of 40 mg/min for 4 min, followed by a maintenance dose of 24 mg/min. The maintenance infusion was continued until 10 minutes post extubation. Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and end-tidal isoflurane levels were recorded at 5 minute intervals during the infusion period and then 5, 15, and 30 min post infusion. If within 10 minutes, the infusion of esmolol or placebo was unsuccessful in controlling the blood pressure (SBP > 50% avg ward pressure or > 180 mmHg) additional antihypertensive medications were added (labetolol or hydralazine). Efficacy was defined as a decrease in SBP to within 20% above the patients average ward pressure (AWP). The need for additional antihypertensive agents to control blood pressure was also used to assess efficacy between the two groups. All data was entered into a Digital Equipment Corporation VAX 11/780 computer using the Viking Data Entry System. All statistical analyses were performed using SAS version 5.03 (p < 0.05 being significant). Fisher's exact test was used to test the overall usage of additional antihypertensive agents and for efficacy of treatment between the two groups.

Results. Within 3 minutes of starting the

Results. Within 3 minutes of starting the esmolol and throughout the infusion period, SBP was

significantly lower than that of the placebo group which continued to climb until additional antihypertensive medications were added. During the infusion period, 20/21 (95%) of the esmolol treated patients had SBP return to within 20% of AWP, 18/21 (86%) were within 15% AWP, 16/21 (76%) were within 10% AWP, 14/21 (67%) within 5% AWP, and 10/21 (48%) returned to AWP.

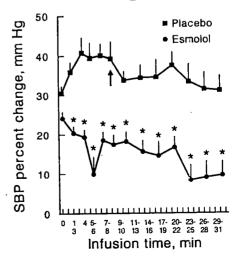
The esmolol group had significantly fewer patients (1/21, 5%) than the placebo group (14/19, 74%) who required intervention with additional antihypertensive agents to control SEP. A significant decrease in HR was also noted in the esmolol treated group. Two patients required discontinuation of esmolol due to mild to moderate hypotension and one dose was modified because of a nodal rhythm.

Discussion. Hemodynamic control is an integral part of the postoperative management of the neurosurgical patient. This study demonstrates that esmolol can be used effectively to control hypertension which develops upon emergence from general anesthesia in the neurosurgical patient.

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> Systolic Blood Pressure Change from Average Ward Value (mean + SE)



t additional antihypertensive agents given significantly different from placebo (p < 0.05)

THE RELATIVE VALUE OF DIFFERENT NEUROPHYSIOLOGICAL MONITORS IN A RHESUS MONKEY MODEL OF CEREBRAL ISCHEMIA J. Gilbert, FFARCS, R Firsching, MD, L Bunegin, BS, J Gelineau, BS

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Introduction: A simple measure of total EEG power has been shown to be a useful indicator of cerebral electrical activity and EEG power monitoring during controlled hypotension has been recommended. Implementation of that recommendation will depend upon availability of an economical, easily interpretable monitor which will reliably warn that cerebral ischemic damage is imminent. Some workers have challenged the clinical value of this recommendation because it is unclear what a moderate decline in EEG power actually means. This study compared changes in the power levels of the PSA-1+monitor (Neurologics, Inc.) with raw EEG, short latency somatosensory evoked response (SER) and brain stem auditory evoked response (BAER) utilizing a Pathfinder II (Nicolet).

Method: 12 mature and conditioned Rhesus monkeys were divided into an ischemic (I) group and a hypotensive (H) group. All animals were anesthetized with ketamine hydrochloride 10 mg/kg/lM, removed from their cages and arterial (peripheral and left ventricle) and venous (7 French Swan-Ganz) lines inserted. Anesthesia was maintained with pancuronium bromide 0.05 mgm/kg/hr, 50% N20 in 02, and halothane 0.5-0.6%. Normocarbia was maintained utilizing a Harvard animal pump and the animals were prone with the head elevated in a stereotactic frame. ICP monitoring was by cisternal puncture. Processed and raw EEG monitoring was two channel utilizing electrodes positioned at F_3 , F_4 , P_3 , P_4 and F_z (int. 10-20 system). SER involved median nerve stimulation (200 usec, 20 mA, 128 repetition at 5.7 Hz) and a montage of F_z (ground) to C₂ and F₂ to contralateral central. BAER utilized a stimulus of 95 decibel alternating rarefaction and condensation 200 usec click at 11.1 Hz, 256 repetitions and masking of the contralateral ear with white noise. The montage was $\mathbf{C}_{\mathbf{Z}}$ to ipsilateral A with Fz as ground. Data was recorded on a Grass 7D or the printer of the Pathfinder and PSA. Cerebral blood flow (CBF) measurements was with a total of 2,000,000 radioactive microspheres divided into 4 different and non-overlapping energy spectra injected through the (L) ventricle line and the catheter was flushed with 10x its volume of saline after each injection. In group H reference values including CBF were recorded (Ref) and the mean arterial pressure (MAP) was lowered by infusing esmolol 100 ugm/kg/min, withdrawing 10 cc/kg of plood and placing the operating table in increasing reverse Trendelenburg until the PSA-1 showed a 30% drop in the power spectrum (8 units to 5-6 units). At this point (PSA) all variables including CBF were measured, the MAP held constant for 1 hour by altering the tilt and observations repeated (PSA-1 ir). Restoration of the blood pressure was achieved by discontinuing the esmolol, removing the tilt and returning the blood. Observations were repeated (Reperfusion) In group I the same sequence was followed but nitroglycerine and, if required, nitroprusside was added and MAP lowered until the BAER was lost at which time all vasoactive drugs vere discontinued and MAP restored as above.)bservations were taken when the PSA declined 30% (PSA) the raw EEG began to noticeably decrease in implitude (EEG-d), the raw EEG was lost (EEG-a) the

SER was lost (SER-a) and the BAER was lost (BAER-a). All tests of significance are paired to tests with correction for repeated measures where appropriate. Results: Mean body temp in group I was 37.0C and in group H 37.6. Decline in temperature during the experiment was 1.4° in each group. Duration of the experiment from PSA to Reperfusion was 87 minutes in group I and 86 in group H. Group I animals evidenced neuronal damage with CSF K+ rising from 2.2 to 4.2 meq, (p=0.03) vs a change of 0.1 mEq in group H (p=.690). The PSA readings during group I reperfusion were 9% of reference levels vs 95% in group H and neither the SER or BAER returned to normal in the I group. It is evident from the CBF and cerebral O2 transport (D·O2) figures for reperfusion of group I that post-ischemic cerebral hypoperfusion is present vs cerebral vasodilatation in group H (p<0.02), and vs reference levels in group I (p<0.02) (see tables).

Conclusion: A 30% reduction in PSA power level is equivalent to a 51% reduction in CBF and a 46% reduction in cerebral D.O2. Holding the blood pressure at PSA level for one hour resulted in . cerebral vasodilation. Ignoring the PSA and raw EEG and taking the blood pressure down to loss of BAER resulted in apparent cerebral ischemic damage. Based upon known values of CMRO2 it is likely that neuronal ischemic damage occurred at a D.O2 represented by the SER-a or below. It would appear that limiting falls in CPP and $D \cdot O_2$ to that represented by a 30% reduction in measured global power of the processed EEG provides an adequate 'safety cushion" over one hour to avoid ischemic damage but that taking these values down to the point of increased latency and loss of amplitude of the SER or complete loss of the SER (the two occurred almost simultaneously regarding changes in CPP) places the brain at the very threshold of ischemic damage.

Ischemia Group -- Mean and (SD)

	REF	PSA Gro	(from	EEG-d	EEG-a	SER-A	BAER-a	REPERFUSION
HB	[82.5 (18	3.1) 28	(5.9)	[24 (7.0)	20.2 (6.6)	[20 (7.4)	14 (3.7)	[78.2 (29.9)
CPP makig	74.9 (17	7.9) 23	(3.5)	[[20.2 (4.8)]	1 15.3 (3.6) 	14.8 (3.4)	 9.1 (4.2) 	160.4 (4.2)
CBF*	89.3 (26	5.6) 42.3	(16.9)		ļ	 34.7 (20.4)	20.7 (10.0)	[39.7 (20.0)
D-02	110.3 .3	71 4.7	(1.5)		<u> </u>	[2.7 (1.5)	11.4 (0.6)	13.3 (2.1)

Hypotensive Group - Mean and (SD)

	I REF I PSA I	 1	IPSA - 1 hr	!REPERFUSION!
HAP mmHg	[83.5 (21.8) [29.5 (2.3)]	 	 31.8 (0.4)	
CPP mmHg	75 (21.2) 23.3 (5.2)	 }	 27 (1.2)	67.3 (17.8)
CBF*	72.8 (33.8) 42.3 (16.9)	 	 50.3 (24,4)	1 (64.9)
D 02+	19.8 (3.3) 4.7 (3.5)	 <u> </u>	 15.2 (2.4)	110.8 (6.0)
*mls/10	00gm/min			

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TITLE: ONSET, DURATION AND REVERSAL FOLLOWING DOXACURIUM CHLORIDE (BW A938U) WHEN COMBINED

WITH ISOFLURANE

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INTRODUCTION: BW A938U is a new non-depolarizing muscle relaxant with a long duration of action and minimal cardiovascular side effects. At its E.D.95 it has a relatively slow onset of action (12 minutes) and a duration of 84 minutes when combined with nitrous oxide-narcotic anesthetic. This study was designed to assess the onset time, intubating conditions, duration, and reversal requirements following doses several times the E.D.95 of BW A938U when used with isoflurane anesthesia.

METHODS: Twenty-seven ASA I or II patients, free of hepatic or renal disease, gave written informed consent. The patients received 10 mg of diazepam one hour prior to surgery. Induction of anesthesia consisted of 1 - 2 $\mu g/kg$ of fentanyl and thiopental ℓ - 7 $\mu g/kg$. Once an airway was esablished a Puritan Bennett Myograph 2000 EMG Monitor was calibrated and a stable baseline obtained. Patients were divided into three groups of 9 patients each. Group A and B received 0.05 mg/kg of BW A93EU. Intubation for Group A was at 4 minutes and Group B at 3 minutes following BW A938U administration. Group C received 0.08 mg/kg of BW A938U and intubation was attempted at 3 minutes following drug administration. Anesthesia was maintained with 70% N_20 in oxygen, 0.7% endtidal isoflurane and fentanyl. When the first twitch of a train of four had returned to 25 - 50% of the original twitch height (T_1) a second dose of 10% of the original dose (ie 0.005 mg/kg or 0.003 mg/kg) was administered and repeated each time T₁ returned to the same level of recovery. At the end of surgery neuromuscular blockade was reversed with neostigmine 45 µg/kg or 60 µg/kg, or edrophonium 1000 µg/kg in a randomized fashion. Results are given as the mean ± standard deviation.

Intubating conditions are presented The time to maximum block was $8.1 \pm$ RESULTS: in table 1. 3.3 min. following 0.05 mg/kg and 5.2 \pm 1.4 min. following 0.08 mg/kg. The time for T_1 to return to 5% (n=15) and 25% (n=15) of the original twitch height following 0.05 mg/kg was 65.2 ± 38.8 minutes and 99.1 \pm 23.3 minutes respectively. This was increased to 143.8 \pm 11.7 min. for 5% recovery (n=6) and 209.5 \pm 13.7 for 25% recovery (n=5) following 0.08 mg/kg. Recovery of T₁ from 50 – 90% following (a) 45 μ g/kg neostigmine (n=5) was 7.9 \pm 5.5 minutes, (b) 60 μ g/kg neostigmine (n=7) was 4.9 \pm 3.7 minutes, (c) earophonium 1000 μ g/kg (n=7) was 7.2 \pm 6.0 minutes (n=5). Three of nine patients receiving 45 µg/kg of neostigmine and one of nine patients receiving edrophonium required a second dose of neurostigmine (22 µg/kg) for adequate antagonism of neuromacular blockade. One patient who was still 100% blocked (by EMG but with a second of current who was still and the conduction of the conduction of the conduction of the conduction of current was still and the conduction of the conduction mechanical twitch present) at the end of surgery required a second dose of neostigmine follwing an quate antagonism of neuromuscular blockade. Once adequate neuromuscular function had been obtained.

no patient subsequently had difficulty executing head lift and grip strength tests one hour after the end of the procedure.

<u>DISCUSSION</u>: Increasing the dose of BW A938U above its E.D.95, results in a more rapid onset of neuromuscular blockade. Intubating conditions following 0.05 mg/kg were adequate at 4 minutes, but at 3 minutes, intubating conditions were consistently inadequate. Following 0.08 mg/kg intubation was acceptable at 3 minutes.

When combined with isoflurane for anesthesia, 0.012 mg/kg of BW A938U has a duration (time to 25% recovery) of 32 minutes². In our study, also using isoflurane for anesthesia, increasing the dose of BW A938U to 0.05 mg/kg resulted in increasing the duration to 99.1 minutes, and 210 minutes following 0.08 mg/kg. In several patients having longer surgical procedures, numerous supplemental doses of BW A938U were required. There was no evidence of accumulation with repeated doses in any of these patients. When neuromuscular blockade is attempted at 75% or greater depression of original twitch height, relatively large doses of reversal agent (60 μg/kg neostigmine or 1000 μg/kg edrophonium) may be needed for prompt return of adequate neuromuscular function. The combination of hemodynamic stability, prolonged action, and no cumulative effect provides advantages not evident in presently available non-depolarizing neuromuscular blocking drugs.

Table I Intubation Conditions Following BW A938U

	Grade							
Group	1_	2	3	4				
A	3	4	1	1				
В	0	3	5	1				
С	11	_6	_1	0				

Grade l = passage of tube without coughing. Vocal cords relaxed. 2 = passage of tube with slight coughing and or bucking. Vocal cords relaxed. 3 = passage of tube with moderate coughing and or bucking. Vocal cords moderately adducted. 4 = intubation not possible. Vocal cords tightly adducted.

Group A = 0.05 mg/kg, intubation at 4 minutes. Group B = 0.05 mg/kg, intubation at 3 minutes. Group C = 0.08 mg/kg, intubation at 3 minutes.

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Title: INDUCTION AND MAINTENANCE OF ANESTHESIA WITH PROPOFOL-PROPOFOL INFUSION OR THIOPENTAL-ISOFLURANE

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Introduction. Interest in rapid awakening and orientation after anesthesia has paralleled the movement toward increased safety and the growth of day care surgery. Propofol, a new intravenous central nervous system depressant related to phenol, has a 55 min elimination half life, has proven to be a useful induction agent (1) and is beginning to be used on an experimental basis as a maintenance agemit during infusion in conjunction with N_20-02 , fentan-I or other narcotic and muscle relaxants (2). ProposcI however, has a depressant effect on blood pressure and respiration. The purpose of this investigation was to compare propofol (PROP-PROP) induction and maintenance of anesthesia with thiopental-isoflurare (THIO-ISO) both intra- and postoperatively from bom a vital signs and adverse effects standpoint and for evaluation of speed and quality of recovery.

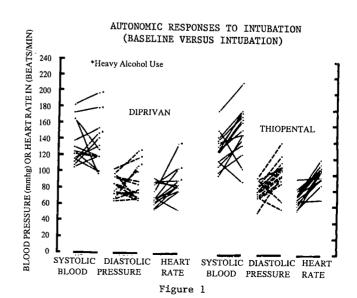
Methods. After approval of the Human Subjects Investigation Committee and obtaining informed consent from 30 ASA I & II patients scheduled for various types of surgery estimated to last 1-3 hours, 15 patients received PROP-PROP (group A) and 15 received THIO-ISO (group B) on a random basis. All were premedicated with morphine (0.1 mg/kg) and, on arrival in the operating theater, received D-tubocurarine (0.05 mg/kg), glycopyrrolate (0.2 mg and fentanyl (1.5 mcg/kg). They then received PROF (2.5 mg/kg) or THIO (5 mg/kg) for induction and when the lid reflex disappeared, succinylcholine (1.5 mg kg) and intubated. Every patient received N_20-0_2 (3L/2L) and fentany1 (up to 1.5 mcg/kg) if the pulsa or blood pressure increased 10%. However, A patients received only a PROP infusion from 0.10-0.20 mg/kg/ min administered via a syringe infusion pump. The ; patients received only isoflurane ranging from 0.05-2.5%. All patients received vecuronium (0.02-0.08 mg/kg) as needed. Adverse reactions were noted plu vital signs including systolic, diastolic and mean blood pressure (SBP, DBP and MP) with an Acutorr, Datascope, heart rate (HR), EKG monitored for arrhythmias and ischemia and PET CO2 (SARA, Allied Instrumentation Lab); these were obtained at regulat intervals ranging from 1 min up to 20 min through the course of surgery. At the end of surgery all patients had their muscle relaxation reversed and were extubated. The times to open eyes, respond to verbal command and to orientation (including name, place and date of birth) were noted. A trained nurse observer blind to the anesthesia given stayed with the patient in the recovery room and noted all rital signs and the ability to recover in addition co Aldrete scores. Any adverse reactions such as emesis were noted. Quality of recovery was judged y the nurse observer.

Results. Ages, weights, heights and anesthesi∈ luration (average 105 min) were similar in groups A ind B. Average induction dose for A was 2.5 mg/kg ind B, 4.9 mg/kg; maintenance for A was 1020 mg by infusion. Average MAC hours of isoflurane was 0.77-twerage SBP was 136 ± 6 and 135 ± 7 during the first inin and 111 ± 4 and 108 ± 5 during the next 25 min for A & B respectively. HR's during the same time intervals for A & B were 81 ± 3 & 93 ± 5 and 74 ± 3

and 82 ± 4 respectively. (p > 0.05) At intubation (see Fig 1) a lower SBP, DBP and HR occurred with propofol. (p < 0.05) Adverse reactions including pain on injection and muscle movements were similar in A & E but there was a 7% and 27% incidence of nausea and vomiting in A & B respectively. Wakeup times were similar including times to open eyes, respond to command and become oriented. Differences however, included the average times in minutes to sit independently and to achieve an Aldrete score of 10; these were 103 & 139 and 30 & 37 with A & B respectively. (p < 0.05)

Discussion. This study in ASA 1 & 2 patients corroborates its similarity to thiopental for induction concerning efficacy, safety, adverse reactions and vital signs. There are some differences concerning maintenance although comparison of propofol to isoflurane, a potent inhalation anesthetic in surgery between 1-3 hours, reveal data yielding few differences. 3P, HR, incidence of arrhythmias, wakeup and orientation times were similar. There were two primary differences: 1) lower HR's and BP's with propofol after intubation, 2) faster times to sit up and achieve Aldrete scores of 10 plus less nausea and vomiting. We conclude that propofol induction and infusion provides an effective and safe alternative to thiopental induction and isoflurane anesthesia, more hemodynamic stability after intubation and a faster, more pleasant recovery.

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Title: USE OF BOLUS ESMOLOL FOLLOWED BY INFUSION FOR INTRAOPERATIVE TACHYCARDIA/HYPERTENSION

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Introduction: Esmolol (E) is a unique cardioselective beta blocking agent with a 10 min elimination half life (1) which is easily managed by intravenous infusion. During anesthesia it has only been used prophylactically in anticipation of tachycardia and hypertension. The purpose of this investigation was to study esmolol intraoperatively for treatment purposes only and to use it with a loading (bolus) dose which would be followed by intravenous infusion using a gravity drip technique.

Methods: This study of 60 patients was approved by the Human Investigations Subcommittee and all patients gave written informed consent. There were two phases. In phase I, 30 patients were chosen as potential candidates who would develop intraoperative tachycardia/hypertension during isoflurane anesthesia in an open label dose ranging study. There were three groups: a) 7 patients had a 0.5 mg/kg bolus followed by a 150 mcg/kg/min infusion using a pediatric infusion drip of 60 drops/ cc, b) 13 patients had a 1 mg/kg bolus followed by a 150 mg/kg/mir infusion and c) 10 patients had a 1 mg/kg bolus followed by a 300 mg/kg/min infusion. The second phase was a double blind, randomized investigation of 30 patients half of whom had an 80 mg bolus (corresponding to 1 mg/kg in an average patient) followed by a 12 mg/min infusion (corresponding to a 150 mg/kg/min dose). The treatment goal was a 15% reduction in 5 min; if unsuccessful, a 40 mg bolus was given followed by a 24 mg/min infusion. Statistical significance was at the p < 0.05 level.

Results: In phase I, all three dosage groups exhibited significant reductions in heart rate (HR) and systolic blood pressure (SBP). Significant reductions in HR occurred within 1 min in groups 2 $(105 \pm 8 \text{ to } 92 \pm 4)$ and 3 $(108 \pm 8 \text{ to } 91 \pm 4)$ and within 2 min in group 1 (100 \pm 2 to 89 \pm 4). Significant reductions in SBP occurred in all three groups within 2 min. The reductions in HR and SBP were not sustained in group 1. In phase II, a bolus

plus infusion dose of esmolol was used which was the amount resembling that used in group 2; 45 sec after bolus-infusion, a greater lowering of mean HR (p < 0.05) with esmolol $(108 \pm 7 \text{ to } 99 \pm 6)$ than with placebo (105 ± 5 to 106 ± 4) occurred. HR with esmolol continued lower for each 15 sec during the entire 5 min period while with the placebo there was no decrease (p < 0.05). The SBP decreases were less dramatic for both esmolol and placebo groups. The rate-pressure product was reduced in the esmolol treated patients during the first three minutes of the infusion when compared to placebo (p < 0.05). Seven placebo treated patients required additional boluses in comparison to only one esmolol treated patient (p < 0.05).

Discussion: In the past esmolol has been shown to be effective and safe for the prophylactic use of tachycardia and hypertension during anesthesia (2). It was therefore used in anticipation but not for therapy. This study proves that esmolol may be safely administered for treatment purposes by an 80 mg bolus followed by an infusion of 12 mg/min. Therefore, it may be used therapeutically during anesthesia. This has important implications since a tachycardia may develop which may lead to ischemia in very poor risk patients. To prepare and administer an infusion with the use of an infusion pump might lead to delays in treating effectively. Rapidity of action will result from the syringe injection described and maintenance by way of infusion. We conclude that a bolus of esmolol combined with the infusion by gravity drip is efficacious, safe and convenient.

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Title: PREOXYGENATION IN THE MORBIDLY OBEST A COMPARISON OF TWO TECHNIQUES

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Introduction: The morbidly obese patient is at increased risk for aspiration of gastric contents due to increased gastric acidity volume and intragastric pressure (1). Rapid sequence induction with cricoid pressure is one technique often utilized in this population to prevent this complication. Either 3-5 minutes of tidal breathing or 4 vital capacity (VC) breaths of 100% 02 provides adequate preoxygenation in non-obese patients and is recommended to avoid hypoxemia before rapid sequence induction (2). Morbidly obese patients, with altered lung volumes and diminished compliance, may respond differently to preoxygenation (3). An earlier study addressed this question (4), however patients served as their own controls and no mention is made of the anesthetic induction technique. We therefore compared two methods of preoxygenation (3 minutes of tidal breathing vs. 4 VC breaths) in the morbidly obese patient undergoing rapid sequence induction and intubation.

Methods: 14 morbidly obese patients (100 lbs > ideal body weight) scheduled for gastric bypass surgery gave their informed consent to this institutional review board approved protocol. All patients received no premedication, had a peripheral IV and 20 gauge radial artery catheter placed under local anesthesia prior to induction of anesthesia. 02 was administered via a close fitting face mask and a circle anesthesia system with a flow of at least 4 liters/min. The patients were randomly assigned to one of two groups. One group breathed normally for 3 minutes while the other group took 4 maximally deep inspirations within 30 seconds. Preoxygenation was followed immediately by induction with thiopental 4 mg/kg IV and succinylcholine I mg/kg IV to facilitate endotracheal intubation. Arterial blood gases were obtained in both groups at three times: 1) baseline while breathing room air 2) immediately after preoxygenation 3) immediately after intubation but prior to ventilation. The samples were analyzed immediately on a Radiometer blood gas analyzer and the results were analyzed for statistical difference utilizing multiple analysis of variance and Duncan's multiple range test. A p value < 0.05 was accepted as statistically significant.

Results: There was no difference between the groups in age, weight or height, nor was there any difference in baseline blood gas values. Both methods of preoxygenation resulted in similar increases in PaO₂ (Table I). The 4 VC breath group had a significantly higher pH and lower PaCO2 following preoxygenation (Table I). After induction and intubation, PaO2 and pH fell in both groups while PaCO2 rose (Table II).

Table I Mean ABG Values After Preoxygenation Pa02 PaCO2 pН %Sat 4 VC breaths 7.43 423.7 33.4 99.8 3' of 0_2 7.38 397.5 41.4 99.4 < 0.05 NS < 0.05 NS

Table II Mean ABG Values Just After Intubation pН PaO2 PaCO₂ %Sat 4 VC breaths 7.37 314.0Ö 42.4 99.65 3' of 02 7.32 318.35 51.1 99.27 < 0.05 NS < 0.05 NS

Discussion: The morbidly obese patient is at increased risk for aspiration of gastric contents (1) and therefore might be subject to rapid sequence induction and intubation. Morbidly obese patients because of decreased functional residual capacity an expiratory reserve volume and elevated closing capacity are at increased risk for developing hypoxemia from V/Q mismatch and shunt (3). Preoxygenation for three minutes or with 4 VC breaths, effectively provides adequate arterial oxygenation throughout rapid sequence induction in these patients. Similar results have been reported for non obese patients and the parturient (2,5). Unlike these other groups of patients, unmedicated obese patients appear to significantly hypoventilate when breathing 100% 02 via a close fitting mask. PaCO2 climbed above 50 mmHg within only 3 minutes after induction and intubation. Therefore, a significant respiratory acidosis had developed (pH < 7.32). Therefore in this group of patients studied, there is the potential of a blunted response to hypercarbia. Ventilation may be even further depressed following narcotic premedication. In contrast the 4 VC breath method encourages hyperventilation and helps maintain normal PaCO2.

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Title: A COMPARISON OF ENDOTRACHEAL INTUBATION CONDITIONS AND RECOVERY FOLLOWING INTUBATING DOSES OF MIVACURIUM

CHLORIDE OR SUCCINYLCHOLINE IN OUTPATIENT SURGERY

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Introduction. Mivacurium Chloride (MIV) is a new short acting nondepolarizing neuromuscular blocking agent with a relatively fast onset and a short duration of action (1,2). There are many clinical situations in which the use of succinvlcholine (SDC) for intubation (INT) may not be desirable and a short acting nondepolarizing muscle relaxant such as MIV might be useful. The purpose of this study was to compare endotracheal intubating conditions, the time of onset of block and spontaneous or induced recovery from maximum twitch suppression following the administration of intubating doses of MIV or SDC in an outpatient population. Methods. 17 ASA Class I-II patients age 22-53 years were studied after obtaining informed consent and institutional review board approval. All patients were scheduled for elective outpatient procedures not expected to be of greater than 1 hour duration and requiring endotracheal INT. Anesthesia was induced in each patient with thiopental (4-6 mg/kg), fentanyl (1.0-1.5 ug/kg) and maintained with 70% N2O and O2. Immediately after induction the ulnar nerve was stimulated with supramaximal train#of#four square wave impulses (0.2 msec duration) of 2HZ every 12 sec via 25 gauge subcutaneous electrodes placed at the wrist. The response was quantitated with a Grass FT10 force transducer and recorded on a Gould polygraph. After establishment of a steady-state baseline train of four, 0.25 mg/kg of MIV or 1 mg/kg of SDC (assigned on a random basis) was administered over 10 seconds through a rapidly running IV. Ventilation was controlled, to maintain a normal end tidal CO2, via mask until INT was accomplished. In the MIV group an investigator blind to the neuromuscular blocking agent administered attempted INT 2 min after drug administration. In the SDC group INT was attempted by the same investigator 1 min after drug administration. In both cases % twitch suppression at INT attempt and intubating conditions were recorded and compared. The conditions were rated on a scale of 1-4 with 1 as excellent and 4 as not possible. When the amplitude of T1 as compared to baseline recovered to 5%, a continuous infusion of MIV or SDC was started and continued until the end of surgery. The initial infusion rate was 10 ug/kg/min for MIV and 60 ug/kg/min for SDC and were adjusted in an attempt to maintain twitch suppression at 95 ± 4% of baseline T_1 . At the termination of the infusion, three of the patients in the MIV Group were allowed to recover spontaneously and the other 6 received necstigmine 0.045 mg/kg and atropine 0.022 mg/kg. Stimulation was discontinued when $\rm T_1$ reached at least 90% of baseline. Time to 90 % block, max block, start of recovery, 5% recovery as well as % recovery at termination of last infusion and time to 75% and 90% recovery after termination of infusion were noted. In the 6 patients who received reversal the \$ recovery prior to reversal and time to 90% recovery after the administration of reversal were noted. The results were analyzed utilizing one-way Analysis of

Variance and Wilcoxin two-sample test. A p value of < 0.05 was considered statistically significant. Data is presented as mean (\pm SD).

Results. There was no significant difference between the groups for age and weight. INT conditions were not significantly different between the 2 groups at the time of INT nor was % suppression of T₁ at INT attempt (Table 1). The time from injection to 90% suppression and maximum suppression was shorter for SDC than MIV (Table II).

The mean time to start of recovery and 5% recovery was almost 2 times as long with MIV but still less than 14 min and 15 min, respectively (Table II). There was no significant difference in the 1 recovery at termination of infusion between the two groups. While the time from the termination of infusion to 75% spontaneous recovery of baseline T_1 was longer in MIV group [9.6 (2.8)min vs 5.8 (2.5)min], this difference did not reach statistical significance, most likely this is due to the small sample size in the MIV group (n=3). However, the time to 90% recovery of T_1 from the termination of infusion was significantly longer in the MIV group [13.2(1.7)min vs 6.6 (3.1)min]. In those patients (n=6) reversed, the mean recovery was 15.2%. In a mean of 6.9 min they achieved 90% recovery. All patients were extubated without difficulty.

Discussion. This study demonstrates that MIV administered in a dose of 0.25 mg/kg allows easy endotracheal INT 2 min after administration with conditions as good as those provided by SDC (1.0 mg/kg) 1 min after administration. Although the time to 90% spontaneous recovery was significantly longer for MIV than SDC it was still short for a nondepolarizing muscle relaxant [13.2 (1.7)min]. Furthermore, reversal from a significant level of blockade (< 20% recovery) was very rapid only requiring a mean of 7.0 min to reach 90% recovery. It therefore appears that MIV might be a useful alternative to SDC particularly in those situations where a depolarizing muscle relaxant may be contraindicated.

Table 1. I	ntubation Data	
	INT Score	% suppression at INT
MIV(N=9)	1.2 (0.4)	90.6 (16.3)
SDC (N=8)	1.1 (0.4)	83.2 (30.2)

Table II. N-M Parameters following bolus administration

Time (min) to:	SDC (N⊨8)	MIV (N=9)
90% Block	0.8(0.3)	1.7(0.7)*
Max Block	1.1(0.3)	2.4(0.9)*
start of recovery	6.4(1.5)	13.2(4.2)*
5% recovery	7.0(1.6)	14.7(6.6)*

^{*} p < 0.05

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Title: INTRAPLEURAL BUPIVACAINE FOR INTRAOPERATIVE ANALGESIA - A DANGEROUS TECHNIQUE?

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Introduction: Several recent studies describe the use of intrapleural bupivacaine (BUP) for analgesia_after thoracotcmy and upper abdominal surgery. BUP was injected through an intrapleural catheter placed at the end of surgery. We report a randomized, double-blinded study in which intrapleural catheters were placed in patients about to undergo thoracotomy. We addressed the following questions: 1) what are the complications of blind intrapleural catheter insertion? 2) what blood levels of BUP are achieved intraoperatively? 3) does intrapleural BUP affect anesthetic requirement?

Methods: After Institutional Review Board approval 18 consenting adults requiring thoracotomy were included in this randomized, double-blinded study. All were given diazepam 5 mg orally before surgery. Anesthesia was induced with thiopental 2-4 mg/kg, fentanyl 2 mcg/kg, pancuronium 0.1 mg/kg, and isoflurane in oxygen. After tracheal intubation the patients were turned with the operative side up and an 18 g Hustead epidural needle (Burron Accu-bloc Perifix Epidural tray) on a saline-filled glass syringe was passed over the sixth or seventh rib posteriorly, medial to the scapula and 3-4 cn above the intended incision line. The needle was directed anteriorly toward the corresponding vertebral body. During apnea the needle was advanced through the parietal pleura with loss of resistance and the epidural catheter (20 g, closed tip) was inserted to 30 cm. Then either BUP 1.5 mg/kg (0.5% solution) or an equal volume of saline was injected while supine. After 10 minutes the patient was positioned for a standard thoracotomy incision. Upon opening the pleural space the surgeon made a visual inspection of catheter placement. Anesthesia was maintained with isoflurane, oxygen, and relaxant. End-tidal isoflurane concentration was measured by mass spectrometer. For 5 patients, arterial samples were drawn at 5, 10, 20, 30, 60, 120, and 180 minutes and BUP levels were determined by gas chromatography. Pneumonectomy became necessary in 3 patients and they were excluded from the study after inspection of catheter placement.

Results: The bupivacaine (BUP) and control groups (CON) were similar with respect to ASA physical status, age, weight, and duration of surgery (Table 1). Three catheters were found coiled within the chest wall. Seven of 18 catheters were in optimal position without pneumothorax or entry into lung tissue. An additional catheter was intrapleural but the patient had a hemodynamically significant tension pneumothorax. Two other catheters entered lung tissue (less than 5 cm), one due to lung adhesions, and the other associated with a non-tension pneumothorax. The remaining 5 catheters entered lung tissue (range 5-30 cm), one with a non-tension pneumothorax and 2 others coiling entirely inside necrotic tumor. Three of these 5 catheters were inside normal lung tissue (no adhesions). Maximal BUP plasma

concentrations (Cmax) and time of Cmax (Tmax) are shown in Table 2. End-tidal isoflurane concentrations were consistently lower in BUP patients but only at 15 minutes was statistical significance achieved. (Table 3)

Table 1. Patient Characterist		acteristics	(mean <u>+</u> SD)
			Duration of
	Age (yr)	Weight (kg)	Surgery (min)
BUP	57+9	74+15	128+54
(n=7)	(range 46-74)	(52-91)	$(66-\overline{2}14)$
CON	48 <u>+</u> 15	86+15	98+28
(n=8)	(range 23-66)	(61 - 104)	(70 - 145)

Table 2. Arterial plasma levels of BUP

Patient	Cmax (mcg/ml)	Tmax (min)
1	4.37*	60
5	1.39*	60
7	1.37	60
8	2.65	30
10	2.27	20
mean+SD	2.14+1.23	46+19

*Catheter embedded in normal lung.

Table 3. End-tidal Isoflurane % (mean+SD)

time (min): 15 30 45 60

BUP 0.63±0.41* 0.72±0.51 0.65±0.27 0.52±0.30 (n=3)

CON 1.10±0.20 1.05±0.20 0.85±0.32 0.86±0.29 (n=7-8)

*P<0.05 student's T test, compared to CON

Discussion: Intrapleural catheter placement for postoperative analgesia with few complications. Accordingly, some have advocated this technique for analgesia in patients with chest wall injuries or impaired pulmonary function. In our study over half of the catheters were sub-optimally positioned. Within 30 minutes 3 patients had significant pneumothorax. An additional 5 patients had catheters in the lung and were at risk for pneumothorax as well as systemic BUP toxicity. Positive pressure ventilation of the lungs probably accounts for our high rate of complications as compared to others! results with spontaneously breathing patients. Therefore, we do not believe this is a safe technique for seriously ill patients who might need positive pressure ventilation.

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Title: ALTERATION OF BLOOD COMPONENTS WITH HEMODILUTION AND ADMINISTRATION OF WASHED SHED RED CELLS

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<u>introduction</u>. It is becoming increasingly common to harvest shed blood and transfuse salvageable washed red blood cells in order to reduce dependence on bank blood. 1,2 However, little data documents aberrations produced when scavenged red cells, crystalloid, and colloid replace a significant fraction of a patient's blood volume.

Methods. Ten consecutive patients who had given informed consent, scheduled to undergo anterior or posterior spine fusion for scoliosis were included in this local review board approved study. Hemoglobin concentration, platelet count, serum albumin concentration, and prothrombin time were measured pre-operatively, immediately postoperatively, and daily for a week following surgery. To facilitate appropriate fluid therapy, during each procedure a laptop computer displayed a running tally of estimated blood, plasma, and red cell volumes and hematocrit. general the first twenty percent of estimated blood volume lcst was replaced with 6% hydroxyethyl starch and washed scavenged cells as quickly as the latter became available for transfusion. When the estimated hematocrit fell below 30%, either whole blood or packed red cells were transfusec according to the relative need to increase red cell mass or blood volume at any particular time. Normal saline was used for further volume replacement. Bank blood was administered post-operatively according to usual clinical criteria. No patient received albumin, plasma, or platelets.

Results. Blood loss ranged from 39% to 54% of estimated blood volume, with the exception of one patient who lost 176% of his estimated volume. Only this last patient received bank blood during surgery. Hemoglobin concentration fell to and was maintained in the vicinity of 8-9 g/dl, with the postoperative administration of packed red cells.

Platelet counts immediately after surgery ranged from 375,000 to 110,000/mm³. Three patients had values below 150,000 in the recovery room or on postoperative days 1-3. Low values recovered after the third day.

Prothrombin times in the recovery room ranged from 12 to 16 seconds (control 12). All values were normal by the 2nd or 3rd postoperative day.

Serum albumin fell to 1.1 to 2.7 g/dl and remained relatively constant throughout the period of observation.

Discussion. Hemodilution with saline and hydroxyethyl starch and the infusion of scavenged washed red cells sufficed to replace blood loss in the range of 30%-50% of estimated blood volume without the use of bank blood. This presents a clear advantage in terms of avoiding transfusion reaction or the transmission of blood-borne diseases such as hepatitis or AIDS. However, as Silva points out we pay a price when using autotransfusion.³ Since the replacement fluids lack all blood components except red cells, sodium chloride, and water, one would expect a significant hypoproteinemia, throbocytopenia and dilution induced coagulopathy. Our data demonstrate that serum albumin is diminished to a clinically significant degree during surgery, and that this deficit is not restored during the first postoperative week. Furthermore three of these patients had a significant thrombocytopenia during the first few days after surgery, although none had a deficit which would be expected to cause bleeding or require platelet transfusion. Using prothrombin time as a gross measure of the availability of clotting factors no patient had a clinically significant coagulopathy.

These patients demonstrated other problems as well. All had some degree of anasarca, though none had clinically apparent pulmonary edema. Two patients had hemoglobinuria lasting a day without apparent sequellae.

In summary these patients could sustain a significant blood loss and be managed with relatively little or no bank blood. However they suffered loss of platelets and albumin as a result. While no patient in this small group required therapy for this loss, patients with less cardiovascular, hepatic, or hematopoetic reserve might not tolerate the stress as well.

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Title: THE EFFICACY AND SAFETY OF BOLUS DOSES OF DOXACURIUM IN CHILDREN

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Introduction. Doxacurium (BW A938U) is a potent nondepolarizing neuromuscular blocking agent for which safety and efficacy has been demonstrated in adults (1). In a previous study, with the incremental dose technique, the ED95 of doxacurium was determined to be 0.03 mg/kg in children anesthetized with halothane. Presently we report the neuromuscular and cardiovascular effects of bolus doses of 0.03 mg/kg and 0.05 mg/kg of doxacurium in children anesthetized with halothane.

Methods. The protocol for the study was approved by the Subcommittee on Human Studies, Committee on Research and by the Pharmacy Committee of our institution. Written informed consent was obtained from parents and from children 7 years of age and older.

Fifteen ASA Class I & II children 2-12 years of age were studied. Children less than 7 years received rectal methohexital (20-40 mg/kg) prior to surgery; the older children did not receive any premedication. They were anesthetized with N20:02 and halothane. Blood pressure, heart rate, EKG, precordial sounds, 02 saturation, end-tidal CO2 and temperature were monitored. Contraction of the adductor of the thumb to indirect stimulation of the ulnar nerve was recorded on Grass Polygraph via a force displacement transducer, Grass FT-03. Repeated supramaximal train-of-four (2 Hz for 2 sec) stimuli were used at a frequency of 0.1 Hz applied at the wrist with surface electrodes.

Following induction of general anesthesia and stabilization at 0.75-1.25% inspired halothane concentration single bolus doses of 0.03 mg/kg (n=8) or 0.05 mg/kg (n=7) of doxacurium were administered. After a minimum of 5 min endotracheal intubation was performed. Surgical stimulation was kept at minimum following the administration of doxacurium. Pulse rate and blood pressures were recorded at baseline and at 1 min intervals for 10 min. Conditions for endotracheal intubation were considered good if the vocal cords were relaxed and abducted but with the passage of the tube a slight cough occurred. It was considered excellent if no movement occurred during or after intubation. The recovery of the twitch height was followed.

When clinically indicated, patients received incremental additional doses of the relaxant. If residual neuromuscular relaxation was present at the end of the surgical procedure, it was antagonized by the administration of atropine 0.03 mg/kg and neostigmine 0.06 mg/kg.

 $\underline{Results}$. The mean age of the children studied was 5.6 (SE+0.9) years.

In the first eight children receiving bolus doses of 0.03 mg/kg of doxacurium a mean (\pm SE) 90.1(\pm 4.8)% depression of the first twitch of the train-of four (T1) occurred in 6.6(\pm 0.8) min. This dose produced intubating conditions that were considered excellent in two patients and good in the other five. After this dose the twitch response recovered to 25% of control in 25(\pm 6) min, to 50% in 34(\pm 6) min and to 75% in 51(\pm 8) min. The recovery index (25-75%) was 26(\pm 3) min in these patients.

The larger does of doxacurium (0.05 mg/kg) produced 100% depression of the twitch response (T1) in six children and 98% depression in the seventh. The maximum neuromuscular depression occurred in $3.1\pm(0.2)$ min. Conditions for endotracheal intubation were considered excellent in all these patients. T1 recovery to 5% occurred in $26(\pm4)$ min to 25% in $42(\pm4)$ min and 50% in $56(\pm5)$ min.

In the first 5 min after the administration of doxacurium, there were no significant changes in the mean arterial pressure or the heart rate. The maximum percent change in mean arterial pressure after 0.03 mg/kg was 102.1(±6.2)% of control and in heart rate 101.8(±5.6) of control. After 0.05mg/kg the change was 105.2±7.1% in mean arterial pressure and 108±6.3% in heart rate.

<u>Discussion</u>. ED95 doses (0.03mg/kg) and 1.7 times ED95 (0.05mg/kg) doses of doxacurium were very well tolerated by children anesthetized with halothane with no clinical changes in heart rate or blood pressures. Compared to preliminary adult data, children seem to require larger doses of the drug to achieve comparable neuromuscular depression and seem to recover faster.

The onset and duration of action of BW A938 compares favorably with presently available neuromuscular blocking agents (3). The absence of side effects, however, would offer an advantage over the existing ones.

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EFFECTS OF WOUND EXCISION ON PULMONARY HEMODYNAMICS AND GAS EXCHANGE Title: IN BURNED PATIENTS

Authors:

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Introduction: In an animal model, burn wound excision has been found to be followed by a protracted pulmonary dysfunction, characterized by pulmonary hypertension and a decrease in PaO₂ (1). The present study was performed to determine if and to what extent pulmonary hemodynamics and gas exchange are affected by wound excision in burned patients.

Methods: After IRB approval, 11 patients undergoing debridement and skin grafting procedures were studied. Patients' mean + SD age was 36 + 10 years, body weight was 72 + 18 kg, burn size was 53 + 10% BSA, and postburn day of study was 19 + 13. All patients were without significant, pulmonary, cardiag reposit or hearting significant pulmonary, cardiac, renal, or hepatic dysfunction, were not septic, and were not receiving intravenous hyperalimentation. Three patients were studied twice, 2, 13, and 14 days apart, respectively. After pulmonary and systemic arterial catheters were introduced, anesthesia was induced with thiopental, 4-6 mg·kg⁻¹ (followed by vecuronium, 0.1 mg·kg⁻¹, and endotracheal intubation) and maintained with enflurane or isoflurane at end-tidal concentrations of 0.75 MAC in N20:02 with a constant F102 of 0.36-0.45. Mechanical ventilation (tidal volume 10-15 ml·kg-1, rate 8-12 breath·min-1) was used to maintain normocarbia. Lactated Ringer's solution (LR) and packed red cells (PRC) were administered to maintain pulmonary capillary wedge pressure (PCWP) between 6-15 mmHg and hemoglobin (Hb) concentration at about 10 g-dl-1. Serial measurements, including cardiac output, systolic, mean and diastolic pulmonary artery pressures (PASP, PAMP, PADP), PCWP, right atrial pressure (RAP), arterial and mixed venous blood Hb, pH, PO₂, PCO₂, and O₂ contents were made before induction of anesthesia (Stage I, pression), 20 min of the induction of the procession of the p baseline); 30 min after induction of anesthesia (Stage II); at the end of surgery, after wound excision, but still under anesthesia (Stage III); in the recovery room (Stage IV) while the patients were normothermic, hemodynamically stable, were breathing spontaneously, and were not shivering. Cardiac index (CI), pulmonary vascular resistance (PYR), alveolar-arterial oxygen tension gradient (P(A-a)O₂), and venous admixture (Qsp/Qt) were calculated using standard equations. Serum colloid osmotic pressure (COP) was determined before and 12-24 hours after surgery.

Results: (Table) During anesthesia, wound excision was not followed by any significant change in either pulmonary artery pressure nor gas exchange indices (Stage III vs Stage II). Postoperatively (Stage IV), all hemodynamic variables returned to baseline values and again, no deterioration in lung function was detected. The size of wound excision was 21 + 6% body surface area. Intraoperative blood loss was replaced with 5.2 + 1.5 liters of LR and 3.5 \pm 1.5 units of PRC. COP decreased during the study period from 13.7 ± 3 to 9.6 ± 3 mmHg (p < 0.001). At Stage I Hb was 10.4 ± 1.3 g·dl⁻¹, PCO₂ was 38 ± 4.5 mmHg, pH was 7.43 ± 0.03, RAP was 8.2 ± 2 mmHg, and they did not change significantly throughout the study.

Discussion: Baseline PASP and PAMP were abnormally high and associated with an elevated CI and low PVR. During anesthesia, PASP and PAMP decreased in a parallel fashion with CI while PVR remained unchanged. Throughout the study, PADP-PCWP difference was normal, ranging from 0 to 5 mmHg. Therefore, pulmonary hypertension in burned patients appears to be a consequence of the high CI rather than of abnormal pulmonary vasculature. Pulmonary artery pressures and PVR were not affected by wound excision.

Pre-operative gas exchange indices were abnormal despite no significant lung abnormality was detected by physical exam and x-ray. During anesthesia, gas exchange impairment did not further increase and actually was of the magnitude reported in normal patients under the same anesthetic conditions (2,3). No deterioration in gas exchange was observed after surgery, when COP-PCWP gradients were often less than 2 mmHg, suggesting that the large amounts of crystalloids administered to replace blood loss were well tolerated. In conclusion, burned patients were shown to have pulmonary hypertension and abnormal gas exchange, which, however, were not affected by wound excision.

Table: Effects of Wound Excision on Pulmonary Hemodynamics and Gas Exchange in Burned Patients

Variable	Stage I	Stage II	Stage III
CI	6.2 + 0.9	4.3 + 0.8a	4.5 + 0.7a
PASP	32 + 5 . 4	27 + 5.5a	28 + 4.5a
PADP	14 + 3.4	11 + 2.4a	11 + 2.4a
PAMP	20 + 3.6	16 + 3.0a	17 + 2.9a
PCWP	11 + 3.0	9 + 2.0a	10 + 2.3
PVR	60 + 20	66 + 23	68 + 24
PaO ₂	74 + 11	150 + 37	160 + 33
P(A-a)O ₂	26 + 12	76 + 36	68 + 29
Qsp/Qt -	$12.\overline{5} + 7$	$14.\overline{0} \pm 3.8$	$13.\overline{6} + 3.5$
F _I O ₂	0.21	0.38 + 0.02	0.38 + 0.02

Mean \pm SD (n = 14). Stage I, pre-excision, awake; Stage 2, pre-excision, anesthetized; Stage III, post-excision, anesthetized. CI = cardiac index (1·min·m-2); PASP, PADP, PAMP = pulmonary artery systolic, diastolic, and mean pressure (mmHg) respectively; PCWP = pulmonary capillary wedge pressure (mmHg); PVR = pulmonary vascular resistance (dyne-sec-cm⁻⁵); PaO₂ = arterial oxygen tension (mmHg); $P(A-a)O_2 = alveolar-arterial$ oxygen gradient (mmHg); Qsp/Qt = venous admixture (%); $PIO_2 = fraction$ of inspired oxygen concentration. a = p < 0.01 vs Stage I.

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Title:

HAEMODYNAMIC CHANGES DURING EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY UNDER GENERAL ANAESTHESIA.

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Introduction. Extracorporeal Shockwave Lithotripsy (ESWL) may be performed under either regional or general anaesthesia. Epidural anaesthesia is preferable because patients are able to cooperate in their positioning, benefit from prolonged postoperative analgesia and have little constitutional disturbance. However, some patients may not tolerate epidural anaesthesia and for these, a suitable general anaesthetic technique must be chosen. The purpose of this study was to determine which anaesthetic technique (volatile vs. volatile with opiate supplementation) produced minimal haemodynamic changes during ESWL.

Methods Fifty patients ASA I or II and scheduled For ESWL (Dornier system) were randomly allocated to receive either enflurane (E) or fentanyl (F) after institutional approval and informed consent had been obtained. All patients received midazolam 0.03mg/kg and glycopyrrolate 0.005mg/kg 5 minutes prior to induction with thiopentone 5mg/kg and suxamethonium 1.5mg/kg. Subsequently muscle paralysis was achieved with vecuronium 0.1mg/kg and patients ventilated to normocapnia with 66% nitrous oxide in oxygen. Patients in Group A were given up to 2% E and patients in Group B received F 2mcg/kg immediately prior to induction and up to 1% E to ensure unconsciousness. All patients were preloaded with 500 mls. Hartmann's solution in the anaesthetic room. Systolic (SAP) and diastolic (DAP) arterial pressure (Datascope Accutorr) and pulse rate (PR) were recorded awake (I), 5 minutes after induction (II), after positioning on the cradle (III), 5 minutes after immersion in the bath (IV), after commencement of ESWL (V) and continuously at 3 minutes intervals thereafter until the patient responded to command. Hypertension and hypotension were defined as SAP 20% greater than or less than control respectively. the inspired E concentration and in Group B by increaments of F (25mcg). Hypertension in both groups was treated with i.v. fluids and ephedrine. E was discontinued as the patient was removed from the bath. After reversal of muscle paralysis, the time taken for the patients to respond to command was noted. Nausea and postoperative pain were assessed in the recovery room. Statistical analysis was with Student's T test and F test.

Results Patients were well matched with respect to age, number of shocks received, duration of anaesthesia and length of shock treatment. SAP was reduced below control (awake) values when the patient was positioned on the cradle (III) and up to 5 minutes after immersion in the bath (IV) (p<0.05). However, these changes were not significantly different between groups A and B.

23 patients in group B and 20 patients in group A had 27 and 21 episodes of SAP <20% control respectively (not significant). Mean duration of hypotension was longer in group B patients (9.16 + 5.18 min) than group A patients (6.92 + 5.36 min). Two patients in group B required ephedrine to maintain SAP. In group A 16 patients had 22 episodes of SAP> 20% control values compared with 7 episodes in 7 group B patients (p<0.05).

<u>Discussion</u> During both regional and general anaesthesia for ESWL, haemodynamic changes may occur due to positioning of the patient on the cradle, immersion in the bath and stress of the shock waves. (1,(2) It is important to minimise these changes, especially in patients with poor cardiovascular reserve. The results of this study suggest that hypotension (SAP <20% control) readily occurs during positioning on the cradle and immersion in the bath, irrespective of whether an opiate based + volatile or solely volatile anaesthetic technique is used. However, the stress of ESWL (as reflected by an increased SAP) may be attenuated to a greater degree when fentanyl is given in addition to a volatile agent.

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Haemodynamic Changes During ESWL

A	I	11	III	IV	٧
SAP	142 <u>+</u> 18	145 <u>+</u> 22	107 <u>+</u> 19*	105 <u>+</u> 17*	124 <u>+</u> 18
DAP	86 <u>+</u> 13	93 <u>+</u> 12	69 <u>+</u> 11	· 64 <u>+</u> 13	78 <u>+</u> 12
PR	83 <u>+</u> 16	97 <u>+</u> 18	94 <u>+</u> 16	92 <u>+</u> 18	89 <u>+</u> 17
В					
SAP	139 <u>+</u> 18	12 <u>4</u> +15	101 <u>+</u> 18*	103 <u>+</u> 22*	117 <u>+</u> 16
DAP	87 <u>+</u> 10	79 <u>+</u> 10	65 <u>+</u> 10	63 <u>+</u> 15	72 <u>+</u> 10
PR	79 <u>+</u> 16	82 <u>+</u> 16	79 <u>+</u> 14	76 <u>+</u> 15	79 <u>+</u> 12

All results expressed as mean ± SD * p<0.05 compared to control.

Title: PRE- AND POST-JUNCTIONAL INTERACTIONS OF VECURONIUM WITH SUCCINYLCHOLINE IN THE CAT

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Introduction: Vecuronium (Vec) is an intermediate duration nondepolarizing neuromuscular relaxant with known pre-junctional action (1). It has been shown effective in suppressing succinylcholine (Sch) -induced fasciculations (2). This study investigated the pre- and post-junctional interactions of Vec and Sch in the cat.

Methods: Experiments were performed on anesthesized cats weighing 2.0-4.1 kg. Anesthesia was induced with nitrous oxide and halothane and maintained with alpha-chloralose 90 mg/kg iv. Cats were tracheostomized and ventilated to maintain normocarbia. Arterial BP was monitored continuously. Cat soleus neuromuscular preparations were like those of Standaert(3) and Hartman et. al.(4). Isometric contractile tension of soleus muscle was recorded in response to supramaximal nerve stimuli of 8-12 mV and 2.5 ms duration; stimuli were delivered at 0.4 Hz. Vec and Sch were given sequentially by vein. The intensity and time-course of Sch (100 mcg/kg) action was observed before and after various Vec doses (0.625 -10 mcg/kg) were administered (fig. 1). Five minutes elapsed between pretreatment with Vec and Sch administration. At intervals, the nerve was stimulated at 400 Hzx10 sec. to evoke a neurally mediated post tetanic twitch potentiation (PTP)(3). Thus, PTP was used to evaluate motor nerve terminal changes caused by Vec and Sch.

Results: Vec doses at or below 10 mcg/kg did not reduce indirect twitch. Over the Vec dose range of 5-10 mcg/kg administered prior to Sch 100 mcg/kg iv, fasciculations were antagonized in a dose-related manner. When Vec was given in smaller doses (0.625-2.5 mcg/kg), fasciculations were not prevented.

Vec, as a function of dose, reduced PTP. On average the highest Vec dose (10 mcg/kg) reduced PTP to about 1/3 of control, and on occasion, Vec doses of 5-10 mcg/kg abolished PTP.

Over the entire range of Vec doses examined, both depth and duration of the subsequent neuromuscular blockade induced by Sch were antagonized in a

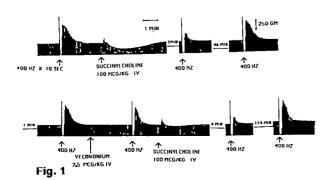
dose-related manner. At the highest Vec doses (5-10 mcg/kg), subsequent Sch blockade was antagonized 50.3% +/- 5.3 (% of control +/- SE). The Sch block duration was also shortened by 53.9% +/- 4.5.

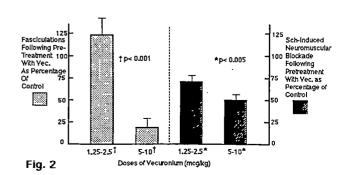
<u>Discussion</u>: These experiments demonstrate Vec's preand post-junctional actions. Vec, acting pre-junctionally, antagonizes repetitive nerve firing induced by high frequency tetanic stimulation, thereby antagonizing neurally mediated PTP. Similarly, Sch-induced repetitive firing of the nerve is antagonized by Vec. Pretreatment with Vec has been utilized clinically to prevent Sch-induced fasciculations and their complications in the operating room. However, Vec's action to antagonize fasciculations without causing twitch depression appears to fall within a narrow dose range (5-10 mcg/kg).

As a function of dose, Vec, acting post-junctionally, antagonizes the depth and duration of Sch-induced neuromuscular blockade. Thus clinically, a larger dose of Sch is required to obtain adequate relaxation.

Sch's pre-junctional effects are more susceptible to antagonism by Vec than its post-junctional neuromuscular blocking effects (fig. 2). This implies that pre- and post-junctional cholinergic receptors differ. The pre-junctional receptors appear more sensitive to Vec's effects.

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TITLE: **AUTHORS:**

Cardiovascular Effects of Mivacurium Chloride in Patients with Coronary Artery Disease B.C. Hall, M.D., B. Baldwin, CRNA, R. I Raymond, P.A.-C, M.M. Abou-Donia, Ph.D.,

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INTRODUCTION:

Mivacurium is a neuromuscular blocking agent currently in clinical trials¹. It has previously been shown to have minimal hemodynamic effects when given at doses up to and including 0.15 mg/kg (\sim 2 x ED95) in ASA I-II patients². We examined the hemodynamic effects of mivacurium in patients with documented coronary artery disease.

METHODS:

Nine ASA III-IV patients aged 47-75 years old undergoing coronary artery bypass grafting (CABG) were studied after obtaining institutionally approved written informed consent. Patients had ejection fractions >.40 as measured by left ventricular angiography and had no evidence of unstable angina. Premedication consisted of a narcotic (morphine 0.1 - 0.2 mg/kg,i.m. or methadone 5-15 mg,p.o.) and a benzodiazepine (diazepam mg,p.o.). Prior to anesthetic induction, pulmonary artery and radial artery catheters were inserted. Anesthesia was induced with intravenous fentanyl (0.1 - 0.25 mg) in successive increments. Intravenous midazolam (0.05-0.20 mg/kg) was administered to augment anesthesia. Intubation was accomplished with intravenous succinylcholine (1.0 mg/kg). 100% oxygen was administered throughout and the patients were ventilated to maintain a normal PaCO2. Ten minutes after intubation, under steady state conditions, 0.15 mg/kg mivacurium was administered intravenously over 60 seconds. Arterial blood pressure, pulmonary capillary wedge pressure, central venous pressure, heart rate and cardiac output were measured at baseline prior to mivacurium and at 2,5 and 10 minutes following mivacurium. Data were compared by analysis of variance.

RESULTS:

Cardiovascular variables (mean ± SEM) are shown below:

	Baseline	2 min	5 min	10 min
Sys BP	123 ± 4	123 ± 4	125 ± 4	124 + 4
Dias BP	60 ± 2	59 ± 2	59 ± 2	59 ± 2
MAP	81 ± 3	81 ± 3	81 ± 3	81 ± 3
HR	55 ± 2	52 ± 2	50 ± 2	49 ± 2
PCWP	13 ± 1	11 ± 1	12 ± 1	12 ± 1
RAP	12 ± 1	10 ± 1	10 ± 1	10 ± 1
CI	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
SVR	2448 ± 185	2699 ± 164	2732 ± 166	2847 ± 242

(Sys BP = systolic blood pressure, mm Hg; BP = diastolic blood pressure, mm Hg; MAP = mean arterial blood pressure, mm Hg; HR = heart rate, ; PCWP = pulmonary capillary wedge pressure, mm Hg; CI = cardiac index, 1.min⁻¹.m⁻²; SVR = systemic vascular resistance, dynes.s.cm⁻⁵)

There was no significant change in any variable with time. There was a notable absence of hypotension and tachycardia. In addition, there was no evidence of myocardial ischemia as determined by ST-segment analysis. DISCUSSION:

Neuromuscular blocking agents may have cardiovascular side-effects that are undesirable in cardiac patients. A previously reported study has shown that rapid bolus administration of 0.20 -0.25 mg/kg (\sim 2.5-3 x ED95) mivacurium results in little or no hemodynamic changes in most healthy (ASA I-II) patients, but is associated with transient hypotension and tachycardia in some patients2. Rapid administration of 0.15 mg/kg (~2 imes ED95) mivacurium was without effect on mean arterial pressure or heart rate in healthy (ASA I-II) patients. Our preliminary data suggest that 0.15 mg/kg mivacurium, given over approximately 60 seconds, was associated with no remarkable car-diovascular effects in patients with coronary artery disease. Further investigation of the cardiovascular effects of mivacurium in patients undergoing coronary artery bypass and valvular procedures is warranted.

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Title:

LOW DOSE INTRAMUSCULAR KETAMINE FOR ANESTHESIA INDUCTION IN YOUNG CHILDREN

UNDERGOING BRIEF OUTPATIENT PROCEDURES

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Introdution. Inhalational induction is a popular technique in pediatric anesthesia; however, it is not always acceptable to young unpremedicated children. There is disagreement among anesthesiologists on whether the use of intramuscular ketamine is an appropriate alternative induction technique in children scheduled for brief outpatient procedures, because of concerns over delayed recovery. This study examines the sedating effect, time to mask acceptance, the recovery and discharge times following the use of low dose intramuscular ketamine (2 mg/kg) as a "premedicant/induction" agent in young children undergoing brief outpatient procedures.

Methods: The study was approved by the institutional Information explaining the protocol was review hoard. available for parents' review. Thirty-five unpremedicated children ages 1-3 years scheduled for bilateral insertion of tympanostomy tubes under general anesthesia were studied. In twenty children, anesthesia was induced by injecting 2 mg/kg of ketamine (100 mg/ml) in the deltoid muscle using a 25 gauge needle. Induction time was defined as the time from ketamine injection until the child became sedated enough to accept a combination of 70% N2O and up to 3% halothane close to, but not touching, his face. The quality of induction was rated as excellent, if the child did not object to the inhaled gases, adequate if there was slight resistance, or unacceptable if the child continued to cry or pushed the mask away. In the remaining 15 patients, induction was accomplished by inhalation of N_2O and halothane. Anesthesia was maintained with N_2O , O_2 and halothane delivered via face mask in all cases. recovery time was defined as the interval from discontinuation of the anesthetic gases until the child met the Post-Anesthesia Recovery Room (PARR) discharge criteria (Aldrete). The discharge time was the time required for the child to meet all routine criteria for release from the hospital. A phone call was made to the parents 24 hrs. postoperatively to inquire about post-discharge complications and/or complaints. The recovery and discharge times in patients who receved intramuscular ketamine induction were compared to those recorded in the children in whom both anesthesia induction and maintenance were accomplished by the inhalation of N2O and halothene using the 2-sample t-test.

Results: The mean age and weight of the patients are shown in the table. The mean induction time following 2 mg/kg of ketamine was 2.7 \pm 0.3 minutes. The quality of the subsequent halothane induction was judged excellent in 61% of cases and adequate in the remaining 39%. There were no unacceptable inductions following ketamine administration. The mean duration of anesthesia and surgery, PARR recovery, and total discharge times for patients in both groups are also shown in the table. There were no incidents of any psychological disturbances that were observed by parents within 24 hrs. of surgery.

Age, weight; anesthesia, surgery, recovery and discharge times for patients who received Ketamine vs. halothane induction (mean \pm SD)

Ketamine (n=20)	Halothane (n=15)	P*
20.7 ± 4.9	24.73 ± 9.66	NS
11.25 \pm 1.65	$\textbf{13.93} \pm \textbf{1.94}$	< .001
$\textbf{16.4} \pm \textbf{4.6}$	$\textbf{20.27} \pm \textbf{5.06}$	<.03
$\textbf{7.25} \pm \textbf{3.0}$	$\textbf{8.53} \pm \textbf{3.38}$	NS
$\textbf{14.5} \pm \textbf{4.9}$	13.93 ± 4.64	NS
74.7 ± 14.1	61.33 ± 21.50	<.04
	20.7 ± 4.9 11.25 ± 1.65 16.4 ± 4.6 7.25 ± 3.0 14.5 ± 4.9	

*2-sample t-test

Discussion:

Inhalational induction is by far the most commonly used technique in pediatric outpatient anesthesia. Successful mask induction, however, requires the patient's acceptance and continued cooperation. Failure to achieve such cooperation is not uncommon, especially in young unpremedicated children. Although the use of intramuscular injections is generally undesirable as a routine practice in pediatric anesthesia, it may be indicated in certain situations. When a struggling child refuses the mask and cannot be managed by an intravenous induction because of lack of accessible veins, a small secating intramuscular injection may be the most humane way to induce sleep. Ketamine is one of the few induction agents that can be injected intramuscularly. Its use in the standard induction doses (5-10 mg/kg), however, results in lengthy recovery time.

Our results show that low dose IM ketamine is an acceptable "premedicant/induction" agent in young children. The induction time is short. Even following very brief surgical procedures, the recovery time is not prolonged when compared to a pure inhalational technique. Although the total discharge time is statistically longer, it is still clinically acceptable. The technique deserves more frequent consideration in the management of "difficult" pediatric patients.

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Title:

PREJUNCTIONAL SUPPRESSION OF SUCCINYLCHOLINE INDUCED FASCICULATIONS BY ATRACURIUM

IN THE CAT

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Introduction.

Succinylcholine (Sch) fasciculations result from its known action to evoke repetitive discharging of motor nerve endings(1). To prevent Sch induced fasciculations clinically, it is a common practice to pretreat with a non-depolarizing neuromuscular blocker. In prior work wa have defined, using a well studied cat neuromuscular preparation, the dose - selectivity and time course of d tubocurarine (dTC) in pretreatment suppression of Sci fasciculations(2). This preparation permits in site monitoring of repetitive activity from motor nerve endings as well as the post - junctional muscle response. Since atracurium has been shown clinically to be effective for pretreatment suppression of Sch fasciculations(3), we have studied atracurium's mechanism of action, dose selectivity, and time course, as we did for dTC pretreatment.

Methods.

Experiments were performed on anesthetized cats weighing 1.5 - 3.0 kgs.. Anesthesia was induced with halothane and maintained with alpha-chloralose 90mg/kg i.v.. Cats were tracheostomized and ventilated maintaining normocarbia. Experimental methods were like those of Riker(4) and Raines & Standaert(5). The contractile tension of soleus muscle in response to supramaximal nerve stimulation at 0.4 Hz. was recorded. In several cats, dorsal laminectomies were performed to enable antidromic recording of motor nerve ending activity via ventral root filaments. Stimulation at 400 Hz for ten seconds evokes post - tetanic repetition (PTR) by motor nerve endings and obligatory post - tetanic twitch potentiation (PTP). This procedure was used to assess notor nerve ending changes in response to Sch before and after pretreatment with atracurium. Fasciculations vere observed grossly and counted as either present or Corresponding discharges in ventral root ilaments were also recorded. Sch (100 μg/kg) was administered intravenously and the time course and depth of blockade recorded. Return of PTR/PTP was used to ndicate recovery of motor nerve endings. With this as a control, the responses in the same cat to the same dose of 3ch following atracurium pretreatment (50 µg/kg iv) were ecorded. Data were analyzed using paired t-tests except or fasciculation data which were evaluated nonarametrically. Statistical significance was accepted at P 0.05.

Results

Pretreatment with atracurium at dose levels below those blocking twitch, suppressed the Sch evoked repetitive discharges of motor nerve endings and, therefore, prevented fasciculations. Similarly, atracurium also suppressed PTR in motor nerve endings. Atracurium pretreatment, like that of dTC, also decreased the blocking potency of Sch and shortened its duration. In some preparations, the sub - twitch blocking dose of atracurium caused slight potentiation of indirectly evoked muscle twitch.

Discussion.

Atracurium's effect to decrease the potency and shorten the duration of the Sch neuromuscular blockade is consistent with a postjunctional competitive antagonism between the two drugs. between the two drugs. The sub - paralytic dose of atracurium also prevented PTR and PTP. Correspondingly, atracurium prevented Sch fasciculations by a prejunctional suppression of Sch induced motor nerve ending repetitive firing. The same mechanism of prevention of Sch fasciculations has been shown for dTC, another ron - depolarizing neuromuscular blocker (2). It is reasonable to assume that other non - depolarizing pretreatment drugs exert their effect by this mechanism, i.e. a selective prejunctional suppression of motor nerve ending repetitive firing.

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Title: ANTAGONISM OF THE VECURONIUM, ATRACURIUM AND Mg++ BLOCK BY METHYLGUANIDINE IN RATS.

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Introduction. Guanidine and methylguanidine (MeGuan)(1) antagonize nondepolarizing muscle relaxants(MR). This antagonism is due to the increase of stimulated acethylcholine (ACh) release(2). MeGuan is markedly increased in the plasma of patients and rats in chronic renal failure and even more so in the muscle and other tissues of the latter species(3). We have observed that, occasionally, the potency of atracurium and vecuronium was significantly decreased in kidney transplant patients. It was the purpose of this study to determine whether concentrations of MeGuan, encountered in the plasma of patients in chronic renal failure, antagonize in vitro the vecuronium and atracurium induced neuromuscular (NM) block.

and atracurium induced neuromuscular (NM) block.

Methods. Male Sprague-Dawley rats of 250 to 350g B.W. were lightly anesthetized with ether and decapitated. The phrenic nerve-hemidiaphragm preparations were suspended in modified Krebs' solution ([CaCl₂]=1.4mM; MgSO_{ll}]=0.9mM) aerated with 95% O₂-5% CO₂. temperature '37° C, pH 7.38-7.42. The hemidiaphragms were stimulated indirectly through the phrenic nerves with supramaximal, square wave impulses of 0.2 ms duration at 0.1 Hz. Optimal resting tension (10 to 15g) was determined in each experiment. After the force of contraction (P), quantitated by an FTO3 transducer and continuously recorded, became stable the individual dose-response of the NM effect of the MR was determined, without, or after 30 min exposure to 27.5 µM (3µg/ml) MeGuan. In other experiments the antagonism of the NM effect of vecuronium and Mg by 60µM MeGuan was observed.

Results. Preliminary addition of 27.5 µM MeGuan to the organ bath caused a slowly developing <10% increase of P. This concentration of MeGuan shifted the lcg dose-response regression lines of both MR to the right (Fig. 1) and increased 150 of vecuronium from 4.4 to 6.4 µM and that of atracurium from 11.9 to 17.7µM. The NM effects of MeGuan-MR combinations were reversed by washout to above control levels. The probable reason for this is that MeGuan, similarly to 4-aminopyridine, is difficult to remove from the muscle. MeGuan 60 µM antagonized the NM effect of vecuronium and Mg (Fig. 2).

Discussion. The results presented indicate that MeGuan, in concentrations which may be present in the plasma of patients in chronic renal failure (3), antagonizes the NM blocking effect of vecuronium and atracurium. This finding explains the resistance to the NM effects of vecuronium and atracurium encountered in patients in chronic renal failure. MeGuan also antagonized the NM effect of Mg++, due to inhibition of the evoked release of ACn. Therefore it is probable that MeGuan, similarly to guanidine and 4-aminopyridine, antagonizes the NM effect of vecuronium and atracurium by facilitating evoked release of ACh (2). Determination of plasma MeGuan is not a commonly available test. Lacking this information the anesthetist must be prepared to use larger than the conventional intubating doses of nondepolarizing MR and to determine both the intubating and maintenance doses of MR by monitoring NM transmission in patients in chronic renal failure.

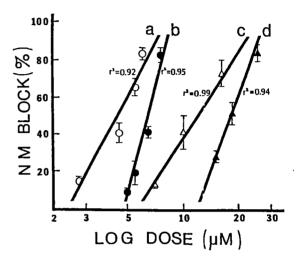


Figure 1. The effect of MeGuan on the dose-response of vecuronium and atracurium. a. Vecuronium; b. MeGuan + Vecuronium; c. Atracurium; d. MeGuan + Atracurium. Note that MeGuan shifts the dose-response regression lines of vecuronium and atracurium to the right.

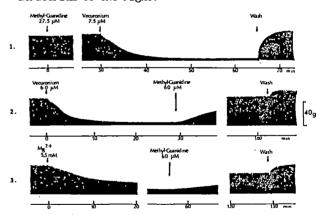


Figure 2. Reversal of the MeGuan-vecuronium block by washout and antagonism of the vecuronium or ${\rm Mg}^{++}$ block by the MeGuan. Note that the force of contraction of the muscle after washout or after reversal of the block by MeGuan is greater than control.

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Title: DETERMINATION OF CARDIAC FUNCTION USI 45 ESOPHAGEAL IMPEDANCE CARDIOGRAPHY

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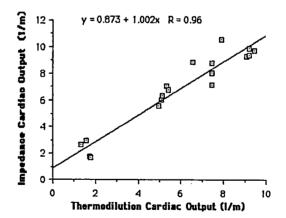
Introduction. There is a need to develop a less invasive and economical way of assessing cardiac function in patients undergoing general anesthesia. The most commonly used method requires the insertior of a pulmonary artery catheter for thermodilution measurement of cardiac output. This procedure is costly, periodic, and potentially dangerous. Other less invasive methods are less reliable and require the use of expensive devices and personnel. This study investigated the use of an esophageal impedance catheter for beat to beat determination of stroke volume and cardiac output in comparison with standard thermodilution technique.

Methods. Five animals (two dogs, 20-25 kg, and three sheep, 47-66 kg) were anesthetized, intubated, and ventilated to maintain their pH, PaCO2, and PaO2 within physiologic limits. Each was placed in the supine position, instrumented with a flow directed thermodilution pulmonary artery catheter, a central arterial catheter, ECG electrodes, and an esophageal impedance catheter. The esophageal impedance catheter was fabricated of a compliant. biocompatible polymeric material. Two circumferential current and voltage electrodes were incorporated in the catheter and spaced such that the proximal and distal current electrodes were in the proximity of the pharynx and diaphragm whereas the voltage sensing eletrodes encompassed the heart. Between the voltage electrodes, a sound collecting chamber was incorporated to provide auscultatory placement of the catheter and for routine heart and breath sounds monitoring. The esophageal impedance catheter was advanced until optimal heart tones could be heard. Cardiac output was measured by thermodilution at end expiration using 10 ml iced)5W (3 averaged samples). Simultaneous measurements by esophageal impedance cardiography were performed 4 to 6 averaged waveforms.) Specific points along the ECG and impedance waveforms were indentified for calculation of preejection period, left ventricular ejection time, heart rate, and stroke volume, and

these values were used to compute the average impedance cardiac output. Cardiac outputs determined bv esophagea1 impedance and thermodilution were compared using linear regression analysis.

Results. Esophageal impedance cardiography compares well with thermodilution in estimation of cardiac output. Cardiac output obtained from esophageal impedance cardiographic measurements ranged from 1.75 to 10.6 liters/minute while that from the thermodilution technique ranged from 1.54 to 9.23 liters/minute. The figure shows the correlation between the two techniques.

 $\underline{\text{Discussion.}}$ This preliminary animal experiment indicates that there is an excellent correlation between thermodilutuion and esophageal impedance cardiography in estimating cardiac output. The esophageal impedance catheter is as easily inserted as a standard esophageal stethoscope and offers the potential for beat to beat assessment of cardiac function in the anesthetized patient.



Title: EFFECT OF ADRENERGIC BLOCKADE ON POTASSIUM FOLLOWING A SUCCINYLCHOLINE BOLUS

OR INFUSION IN DOGS.

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Introduction. Beta-adrenoceptor blockade with propranolol (non-specific), metoprolol (beta-1), and ICI-118551 (beta-2) has been shown to cause a delay in the peak plasma potassium concentration following the administration of succinylcholine in dogs. 1,2 Alpha-adrenoceptor blockade has been demonstrated to increase intracellular potassium uptake in various clinical situations. This study was designed to examine the effects on plasma potassium concentration of combined alpha and beta blockade during succinylcholine administration and the effect of a continuous succinylcholine infusion with and without beta blockade in dogs.

Methods. Nine mongrel dogs were anesthetized with thiopental, 15-20 mg/kg. The trachea was intubated and anesthesia maintained with halothane, 1-1.5% and nitrous oxide 60% in oxygen. Femoral arterial and venous lines were placed, and a continuous intravenous infusion of normal saline at 6-8 cc/kg/hr begun. Ventilation was adjusted to maintain a pH tetween 7.34 and 7.43. At least 7 days elapsed between studies on individual dogs. Each animal was studied five times. Group 1 (control) received an intravenous bolus of succinylcholine (1 mg/kg). Group 2 received a succinylcholine bolus (1 mg/kg), followed by a continuous succinylcholine infusion. Group 3 was given an intravenous propranolo1 bolus (0.25 mg/kg) and continuous infusion of propranolo1 (0.042 mg/ kg/hr) followed by a succinylcholine bolus (1 mg/ kg). Group 4 received an intravenous propranolol bolus and infusion, as described in Group 3, followed by a succinylcholine bolus and infusion as described in Group 2. Group 5 was given labetalol 3.75 mg/kg, as an IV loading dose, followed by a succinylcholine bolus (1 mg/kg). Arterial plasma potassium was measured (Nova 1) before receiving succinylcholine and at 1,3,5,10,15,30,45,60,75,90,105, and 120 minutes after the succinylcholine bolus. Each group contained 5 dogs. An additional two dogs in Group 2and one dog in Group 4 were required because of the development of a metabolic acidosis in three dogs, requiring their exclusion from the study. For each group, the absolute value of plasma potassium at each time was compared to the baseline potassium by two-way analysis of variance and least square means. In all groups, comparison of plasma potassium at each time interval to the corresponding time in the control group was accomplished by oneway analysis of variance and least square means. P 0.05 was considered statistically significant.

Results. The absolute plasma potassium values for Groups 1-5 are shown in the table. In the control group, succinylcholine caused a significant rise in potassium that peaked at three minutes and returned to baseline after 15 minutes. In Group 2 the plasma potassium was significantly higher than baseline by 5 minutes, peaked at 30 minutes, and returned to control by 45 minutes. There was no significant difference between potassium values at any time when compared to the control group. In

Group 3 the plasma potassium peaked at 30 minutes and returned to baseline levels after 45 minutes. The plasma potassium was significantly greater than the control group at 45 and 60 minutes. In Group 4 the plasma potassium rose significantly by 3 minutes, peaked at 30 minutes, and returned to baseline at 60 minutes. The plasma potassium was significantly greater than control at 30,45, and 60 minutes. In Group 5 the rate of rise in plasma potassium was less than the control group. The potassium level peaked at 10 minutes and returned to baseline after 15 minutes. At 3 and 5 minutes the potassium level was significantly less than control.

Discussion. This study confirms the findings of McCammon & Stoelting: propranolol causes a delayed rise and results in higher peak plasma potassium concentrations after succinylcholine administration. The effects of a continuous infusion of succinylcholine on plasma potassium are most likely a result of the continuous depolarization of the motor endplate with subsequent potassium leakage. Since skeletal muscle is the largest reservoir for potassium uptake, beta blockade with propranolol magnifies the effect of a succinylcholine infusion as seen in Group 4. Alpha blockade in the presence of beta blockade markedly diminishes the effect of beta blockade on plasma potassium following succinylcholine, but does not completely abolish it.

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Time	r	11	III	IV	v
(H)	Control	SI	PSB	PSI	LSB
0	3.68±.27	3.86±.18	3.91±.21	3.66±.16	3.33±.36
1	4.17 [±] .47	4.16 [±] .19	4.17 [±] .19	4.06 [±] .24	3.65±.43b
3	4.40±.59a	4.39 [±] .37	4.35 [±] .32	4.22 [±] .25 ^a	3.71±.34b
5	4.12 [±] .37	4.4g±.43a	4.26 [±] .29	4.17 [±] .28 ^a	3.71 [±] .34
10	4.22±.39	4.47 [±] .39 ^a	4.30±.23	4.24 [±] .11 ^a	3.93 [±] .14 ^a
15	4.24 [±] .47 ^a	4.48 [±] .54 ^a	4.53±.36	4.37 [±] .12 ^a	3.84 [±] .11 ^a
30	4.08±.49	4.49 [±] .65 ^a	4.67 [±] .51 ^a	4.62 [±] .29 ^a ,b	3.71 [±] .21
45	3.93 [±] .64	3.94 [±] .62	4.62±.77ª,	b _{4.48} ±.42 ^a ,b	3.56 [±] .29
6 Ø	3.8ر.61	3.74 [±] .44	4.47±.96b	4.34 [±] .48 ^a ,b	3.5ر.32
75	3.61 [±] .48	3.58 [±] .36	4.19 [±] .76	4.10±.39	3.39±.28
90	3.82 [±] .63	3.51 [±] .25	4.20±.78	4.04±.33	3.41 [±] .27
105	3.55 [±] .37	3.51 [±] .25	3.98 [±] .52	3.92±.29	3.47 [±] .19
120	3.58±.30	3.52±.26	3.93±.46	3.90±.26	3.56±.3
T	able I - Ak	solute val	ues of K+	after succiny	
		Mea	n ±sp		

Mean →SD

a Significantly different from baseline (P<0.05)

b Significantly different from control group (P<0.05)

SI = Sux Infusion PSB =Propranolol Sux Bolus
PSI = Propranolol Sux Infusion LSB = Labetalol Sux Bolus

Title: THE INFLUENCE OF ANESTHETIC AGENTS ON MYOCARLIAL TOLERANCE TO TOTAL ISCHEMIA: HALOTHANE VS ISOFLURANE Author: R. Hill, M.D., J. Pollard, B.S., R. Cumming: M.D., J.G. Reves, M.D. and J. Lowe, M.D.

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<u>INTRODUCTION:</u> Controversy exists over the relative influence of halothane and isoflurane on nvocardial ischemia. Clinical and laboratory data have shown that regional ischemia may occur nore frequently with isoflurane, presumably because of differences in hemodynamics and collateral coronary perfusion. It is also possible they exert different metabolic influences that affect tolerance to ischemia. This study compares myocardial tolerance to ischemia measured y prolongation of time required for development of cardiac rigor in the absence of collateral coronary circulation or wall stress. The onset of rigor determined with this model corresponds well with evidence of irreversible cell injury and myocardial ATP depletion.

 $\frac{\text{ETHODS:}}{\text{Inesthetized}}$ Sixteen dogs (14-25kg) were randomly inesthetized with either 1.8% halothane (2 MAC) or 2.6% isoflurane (2 MAC). They were intubated, paralyzed with vecuronium 0.1 mg/kg, and venilated with 100% θ_2 to maintain normocarbia. emoral artery pressure and ECG were monitored. ledian sternotomy was performed to expose the leart. Thirty minutes after induction of mesthesia arterial blood samples were obtained or determination of PaO₂, PaCO₂, pH, hematocrit, erum lactate and glucose, and plasma norepiephrine and epinephrine. The heart was then apidly excised to create total ischemia. A left entricular slab was prepared and incubated in a ater bath to maintain a temperature of 37°C. A ortion of each slab was placed in a compressibiity gauge which identifies the onset of rigor by etecting an abrupt increase in resistance to issue deformation by an intermittantly applied ompressive force of 30mmHg¹. A second subenocardial portion of each slab was instrumented ith a needle-tipped Millar catheter continuously ransduced to measure peak myocardial tissue ressure. A third portion of each slab was used or intermittant tissue sampling and HPLC assay f high-energy nucleotide levels every 15 minutes ollowing cardiac excision. Comparisons of indiidual parameters were made by one-way analysis f variance. Time-dependent declines in highnergy nucleotide levels were compared by analyis of variance with repeated measures of log evels. Results are reported as mean <u>+</u> standard eviation.

<u>ESULTS</u>: There were no differences in heart ate, mean arterial pressure, serum glucose or actate, hematocrit, arterial PO2, PCO2, pH, or lasma catecholamines between the two groups rior to cardiac excision. The time required for evelopment of cardiac rigor measured by the ompressibility gauge was significantly greater n the halothane group than in the isoflurane

group (68 \pm 7.2 vs 60 \pm 5, p <.05). The onset of ischemic contracture in subendocardial slabs determined by time to peak tissue pressure measurement tended to be prolonged in the halothane group compared to isoflurane dogs (64 + 6.9 vs 57 + 6.8)p=.08). Analysis of tissue assays of high-energy nucleotides revealed a decline in ATP levels over time of ischemia in both groups (Fig. 1). Timedependent ATP levels were greater in both subendocardial (p <.01) and subepicardial (p <.01) specimens of the halothane group compared to the isoflurane group. There was a progressive increase over time in tissue lactate levels in all dogs with no significant differences between groups.

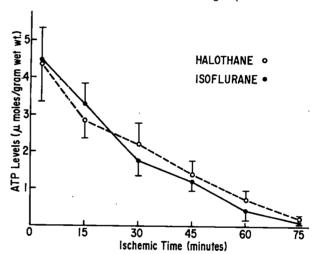


FIGURE 1: Subendocardial tissue levels of ATP as a function of ischemic time. There was a small but statistically significant trend of ATP preservation in the halothane group compared to the isoflurane group (p <.01, analysis of variance with repeated measures of log ATP levels). Mean \pm SD.

<u>DISCUSSION</u>: The data show that halothane, when compared to isoflurane, increases myocardial DISCUSSION: tolerance to total ischemia independent of effects on hemodynamics or collateral coronary circulation. Halothane probably influences cellular metabolism in a way that preserves high-energy nucleotide stores and renders myocardial tissue less vulnerable to injury during complete ischemia.

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CAN GLOBAL CARDIAC PERFORMANCE BE INFERRED FROM THE ARTERIAL WAVEFORM?

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Introduction. Clinicians continue to be intrigued by the prospect of assessing cardiac performance from the contour of the arterial pressure trace. Prior to the advent of cardiac catheterization, numerous investigators attempted to derive cardiac output from the contour of the arterial pressure trace. 1,2 Many patients undergo surgery requiring arterial catheterization for hemodynamic monitoring. However, the use of a pulmonary artery catheter is not always warranted in these clinical situations. Under these circumstances the area under the arterial wave trace is often utilized as an index of cardiac performance. To date, no study has demonstrated the ability of the area under the arterial pressure trace to correlate with cardiac output as an indicator of myccardial function. Therefore, we designed a prospective study to determine whether the area under the arterial wave trace may be used as a valid method for assessing global cardiac function as expressed by cardiac output.

Methods. Following approval of the Human Investigation Committee, twenty-two (N = 22) patients undergoing elective surgery, who required the insertion of an intra-arterial and pulmonary artery catheters for monitoring were studied. Patients who were not in sinus rhythm, who had hemodynamically significant valvular heart disease or who required an intra-arterial balloon were excluded. The radial artery pressure was obtained from a percutaneously placed 20 gauge $\rm Jelco(R)$ catheter. The catheter was connected to an American Edwards disposable transducer (Model 53-DTS-260), by high pressure tubing with a continuous Pharmaseal $^{(R)}$ flush device. The resonant frequency and damping coefficient was determined for each patient study. Thermodilution cardiac outputs (CO) from a Swan Ganz catheter were obtained in triplicate with a Model 9520 Edwards Laboratory Cardiac Output Catheter. For each patient, a minimum of 3 sets of data were obtained. The area under the arterial wave form was determined manually and verified in duplicate. Systemic vascular resistance (SVR) was calculated as MBP - MRAP/CO. Data were presented as mean + SD. Statistical analysis performed using the coefficient of correlation (P 0.05) considered significant.

Results. One hundred fourteen sets of data were collected from these 22 patients. Values for cardiac output ranged between 2.3-6.8 L/min (mean 4.2 + 1.1 L/min) and the area under the arterial wave form ranged between 72-156 (mean 9.4 \pm 11.2). No statistically significant correlation was found between the area under the arterial pressure trace and cardiac output (r = 0.36, P = NS).

Figure I demonstrates two patients with similar cardiac outputs, but different areas under their respective pressure curves. Similarly, Figure 2 reveals two curves with differing cardiac output but similar areas under the curve.

In addition, no correlation could be shown between SVR and the area under the curve within individual patients (r = 0.26, P = NS). Further, no correlation could be demonstrated between changes in the area under the curve and cardiac output (r = 0.38, P = NS).

Discussion. On the basis of our data, we were unable to detect any significant correlation between the area under the arterial waveform and the cardiac output. Even within the same patient changes in cardiac output were not reflected as changes in the area under the arterial waveform. Clinicians have attempted to extend the work of Frank who developed a model aimed at deriving cardiac output from the arterial pressure trace. 2 However, Remington et al. demonstrated that due to the variability of altered wave reflection, determination of cardiac output from the arterial waveform is unreliable. Therefore, on the basis of our data, caution should be exercised in attempting to utilize the contour of the arterial waveform as an indication of global cardiac performance.

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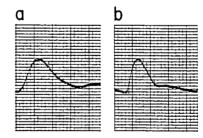


Figure 1. Waveform tracing from two patients with similar CO. (a = 4.2 L/min, b = 4.6 L/min), but with differing areas. a = 82, b = 41.

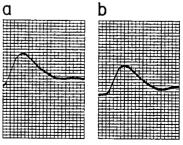


Figure 2. These patients had differing cardiac outputs (a = 2.6 L/min, b = 4.0 L/min), but similar areas under their arterial wave forms. (a = 58, b = 63).

A RAPID AND RELIABLE METHOD OF SELECTING ENDOTRACHEAL TUBE SIZE IN CHILDREN

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Introduction: The selection of an appropriately sized endotracheal tube (EIT) for airway management in pediatric patients is a critical procedure. Anesthesiologists and emergency room physicians would benefit from a system of ETT selection that would provide first choice accuracy. Many times knowledge of the child's weight and/or age is unavailable and in an acute emergency recall of the various formulae for ETT sizing is difficult. The current study is both retrospective and prospective. The retrospective aspect was to determine which anthropometric measurement in children [body weight (bw), age, body length (1), neck circumference (nc), fifth fingernail width (ffw), fifth finger distal interphalangeal joint circumference (ffdic) or nostril diameter (nd)] was the best predictor of appropriate ETT size. An appropriately sized ETT is defined as that ETT which has an air leak between 20-40 cm H₂0. The prospective aspect was designed to verify the accuracy of the "best" predictor (body length) which was identified in the retrospective study.

Methods and Results:

- 1. Retrospective Study 200 children (birth-12 years of age) coming for surgery were intubated with an uncuffed ETT until an air leak between 20-40 cmH₂0 existed. All children had anthropometric data recorded as described above. Correlation coefficients were calculated between correct ETT size and all seven (7) anthropometric measurements. Body length had the best correlation coefficient (r) of 0.95 (Figure 1). The r value for bw, age, nc, ffw, ffdic and nd were all < .90.
- 2. Prospective Study 200 children (birth-12 years) coming for surgery were intubated with an ETT whose size was determined based on each child's body

length (cms). A tape measure was designed that could be held against each child and the ETT size was read off directly [Pediatric Airway Management System [TM.**]. All 200 children were intubated with an appropriately sized ETT (i.e., air leak at 20-40 cmH_ $_2$ 0). The tape measure predicted correct ETT size in 100% of these children on first ETT size selection. This study had IRB approval.

Conclusions: Body length is superior to any other anthropometric measurement or existing formulae in allowing for rapid selection of a correct ETT size in children. A tape measure system as described will allow the anesthesiologist and emergency physician to rapidly and reliably select the correct ETT for children with need for very little input data (i.e., bw, age, or need for formula recall) on first ETT size selection.

*PLANE III, Inc., P. O. Box 14, North Marshfield, Massachusetts 02059

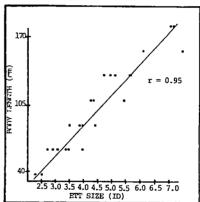


Figure 1 - Endotracheal tube size (ID) vs body length.

Title: THE VOLATILE ANESTHETICS, HALOTHANE, ENFLURANE, AND ISOFLURANE INTERFERE WITH NORMAL

MYOCARDIAL RELAXATION

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<u>Introduction</u>. Relaxation is an important determinant of diastolic filling of the ventricle, and is easily interfered with in early stages of heart disease as well as by pharmacological interventions (1). The purpose of this study is to assess the potential effects of halothane (H), enflurane (E), and isoflurane (I) on the time course and loadsensitivity of myocardial relaxation.

Methods. Twenty-seven papillary muscles of the right ventricle of adult male ferrets were mounted in a temperature-controlled (30°C) chamber closed to the ambient atmosphere and that contained a physiological salt solution (mM): Na+ 135; K+ 5; Ca2+ 2.25; Mg^2+1 ; Cl-103.5; HCO_3 24; $H_2PO_4^2-1$; SO_4^2-1 ; acetate-1 20; glucose 10, continuously bubbled with 95% O_2 - 5% CO_2 (500 ml/min). Muscles were held between a force-length servo transducer (Innovi, Belgium), and a subminiature lucite clip with a built-in stimulation electrode (stimulus interval 4 seconds, 10% above threshold). After stabilization, load-sensitivity of relaxation was determined prior, during, and after exposure to cumulative doses of H (n=9 muscles), E (n=9), and I (n=9). Anesthetic vapor was added to the gas mixture by means of an in_line vaporizer in increments of 0.25 MAC up to 1.5 MAC of H and E and up to 2.00 MAC of I. Vapor concentrations were set in the gas phase with a calibrated acoustic detector. Muscles contracted isotonically throughout with the initial muscle length set at L_{Max} . After reaching steady state at 15 minutes in each anesthetic concentration, load sensitivity of relaxation was determined from an isometric twitch and from a series of six afterloaded isotonic twitches against different afterloads. Force and time coordinates at the onset of isometric relaxation of afterloaded isotonic contractions relative to those of the isometric twitches define a relative time $(\frac{c}{d})$ versus force $(\frac{a}{b})$ relationship, the slope $(\frac{c}{a/b})$ of which is a measure of load-sensitivity (Figure 1).

<u>Results.</u> Relaxation of mammalian ventricular cardiac muscle became less sensitive to load with H, E, and I in a dose-dependent reversible manner. The decrement of load sensitivity per unit of MAC was smaller for I than for either H (p<0.001) or E (p<0.001) (one-way ANOVA on slopes of linear regressions, Figure 2). Withdrawal of anesthetic restored load-sensitivity of relaxation completely within 15 minutes.

<u>Discussion</u>. The decrease in load-sensitivity of relaxation with H, E, and, to a lesser extent, with I, was due to an abbreviation of isometric relaxation of the isometric twitch and a prolongation of isotonic twitches at low loads (Figure 3). The faster isometric relaxation with H, E, and I is consistent with a decreased affinity of troponin C for Ca^{2+} and/or a reduced myofibrillar responsiveness to Ca^{2+} . Since less Ca^{2+} remains bound to myofilaments after a period of shortening than after a comparable period of force development (2), the prolongation of isotonic lengthening observed at all loads below isometric may result from a relative inadequacy of

calcium sequestering systems. Interference with normal myocardial relaxation by volatile anesthetics may account, at least in part, for the hindered diastolic filling of the intact heart (3).

Dr. Housmans was a Parker B. Francis Investigator in Anesthesiology for 1986. Supported by I.A.R.S., Puritan—Bennett Foundation, USPHS GM36365, and Mayo Foundation.

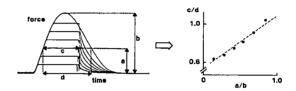


Figure 1

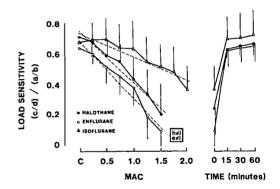
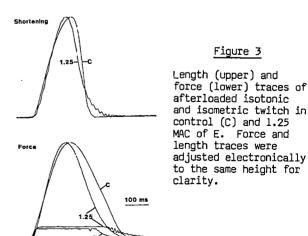


Figure 2



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- 3. Tamura T et al. Anesthesiology 65:A61, 1986.

TTTTE:

PULSE OXIMETRY FOR EVALUATION OF RADIAL AND UINAR ARTERIAL BLOOD FLOW

ATTHORS:

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INTRODUCTION: Radial artery cannulation is a routine procedure in operating room and intensive care units for continuous monitoring of arterial pressure. Complications of this monitoring include hematoma formation, thrombosis, arterial laceration or dissection of the arterial intima, and trauma to the surrounding tissues. The Allen test is the most commonly employed test of forearm arterial perfusion, but its results can be difficult to interpret. The pulse oximeter is a noninvasive monitor that measures arterial hemoglobin oxygen saturation (SaO₂)_{1,2}It can also be used to demonstrate blood flow We evaluated pulse oximetry as a means to assess radial and ulnar arterial blood flow comparing a simple occlusion test (SOT) to the

Allen test (AT). METHODS: This study was approved by the Committee on Research Involving Human Subjects (CORIHS) of the State University of New York at Stony Brook. Informed consent was obtained from 48 volunteers. Each subject then underwent three sequential phases of testing, for which a Nellcor pulse oximeter (Nellcor Corp., Hayward, CA) was used. In the first phase, the adult finger sensor of the pulse oximeter was sequentially attached to the thumb and to the little finger of both hands to obtain baseline SaO, values and rule out a discontinuous superficial palmar arterial arch. In the second and third phases of testing, data obtained by pulse oximetry (PO) was compared to visual observation of palmar arterial reperfusion (Palmar flush (PF)) during both the simple occlusion test and the Allen test, respectively. In the second phase, the simple occlusion test was performed. In order to evaluate patency of the palmar arterial arch, pulse oximeter was applied to the thumb. Then radial and ulnar arteries were simultaneously compressed until the pulse oximeter (in the fast mode) monitored zero saturation, (usually 1-2 seconds) i.e., no arterial blood flow. Digital compression of the ulnar artery was released and the time intervals noted for return of the previous oximeter reading and for visual return of blood flow to the hand (palmar flush). The test was terminated if after 60 seconds arterial blood flow had not returned. The sensor was then applied to the little finger of the same hand, but now the radial artery was released with notation of the same time intervals. In the third phase, the AT was performed bilaterally using the pulse oximeter as in phase 2. The finger sensor was first applied to the thumb and the radial and ulnar arteries were digitally occluded. At that time, the subject repeatedly clenched and unclenched the fist for approximately 15-20 seconds, and then relaxed the hand. As soon as the pulse oximeter indicated an SaO2 of zero, the ulnar artery was released. Return of the previous SaO₂ reading and the occurrence of PF were timed. The sensor was next applied to the little finger for a similar testing sequence of radial artery flow. Finally, subjects with positive indication of abnormal radial or ulnar

artery blood flow were retested one week later to rule out a transient vasospasm. This experiment was similar to the third phase of testing except that, following arterial compression, the ipsilateral artery was released, e.g., the radial artery was released if the sensor had been applied to the thumb.

All reperfusion times were categorized into 3 groups: normal (less than or equal to 5 seconds), equivocal (6-15 seconds) and abnormal (greater than 15 seconds).

RESULTS: A total of 48 subjects, 34 men and 14 women, were studied. Their mean age was 32.3 years, with a range of 23-64 years. One subject had undergone bilateral radial artery cannulation twelve years before and another had a percutaneous arterial blood sample taken eight months earlier. Two patients were known to have Raynaud's disease, and in a third it was suspected.

In phase 1, baseline Sa0, values ranged from 94-100% with a mean saturation of 97.2%. Eight subjects with initially abnormal reperfusion times as measured by both PO and PF were reevaluated. Of these, two individuals again had abnormal reperfusion times by PO and PF, and one had an abnormal PO reading but had an equivocal value by PF.

In phase 2, the SOT was performed using both the PO and PF. Reperfusion times obtained by PO, ranged from 1-10 seconds. PF reperfusion times ranged from 0-5 seconds. No abnormal reperfusion times were obtained by either test. Phase 2 yielded a 100% correlation between PO and PF. In phase 3, the AT was performed using both PO and PF. Both 20 and PF reperfusion times ranged from 1-60 seconds. PO revealed 3 hands with abnormal reperfusion times, whereas observation of palmar flush yielded abnormal reperfusion times in 2 hands (2%). Linear regression analysis shows excellent correlation (r=0.94) between PO and PF as determinants of normal and equivocal palmar reperfusion times when considered as one group. DISCUSSION: The predictability of an abnormal reperfusion time based on pretesting history was very low. The two patients who had abnormal AT results had negative histories. Only one of the two subjects with known vasospastic disease (Raynaud's) revealed abnormal ulnar flow upon initial testing, and a repeat Allen test, after several days of avoiding consumption of coffee and exposure to cold, was normal. This study allows two conclusions. The simple occlusion test yields similar information as does the Allen test and does not require the subject's cooperation in clenching and unclenching his fist. It can then be used when the patient is anesthetized or severely ill. Further, pulse oximetry whether combined with the Allen test or the simple occulusion test has the distinct advantage of providing objective data. REFERENCES

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PRELOAD ADMINISTRATION PREDICTED BY NITROGLYCERIN INFUSION PRIOR TO NARCOTIC INDUCTION

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Introduction. In cardiac surgical patients who do not have optimum intravascular volume, narcotic induction, though not affecting the myocardium directly, can reduce blood pressure. The presence of a high sympathetic tone prior to surgery may mask a decreased venous capacitance. Nitroglycerine in the lower dose ranges may, by dilating venous reservoirs, be provocative in revealing decreased intravascular volume. Echocardiography is a direct method of estimating left ventricular volume. This investigation studied if a prevolume loading test with NTG could establish decreased intravascular volume and if volume loading prior to induction could maintain left ventricular end diastolic diameter (LVEDD) and blood pressure.

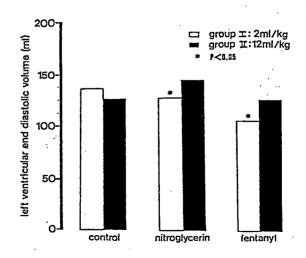
 $\underline{\text{Methods.}} \quad \text{Following institutional approval,} \\ \text{informed written consent were obtained from 8}$ patients undergoing elective coronary artery bypass graft surgery with ejection fractions greater than 50% having no valvular involvement. All patients received their usual cardiac medications along with lorazepam 0.04 mg/kg and morphine 0.1 mg/kg as premedication. A radial artery catheter was used to follow blood pressure changes. Pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and central venous pressure (CVP) were measured using a pulmonary artery catheter inserted through the right internal jugular vein. The Mmode ultrasound data were obtained using a 2.25 MHz medium focused transducer placed at the lower left sternal border and recording the short axis area at the level of the mitral valve leaflet tips at end LVEDD was measured from three exhalation. consecutive sirus-conducted heart beats, converted to volumes. Patients were randomly assigned to receive either 2 ml/kg (group 1), or 12 ml/kg (group 2) preinduction hydration of 0.9% sodium chloride over a 20 minute period. Baseline hemodynamic variables were recorded immediately after insertion of the pulmonary catheter. Echocardiographic and hemodynamic measurements were recorded before hydration, 5 minutes after the start of NTG infusion, and at narcotic induction, following a stabilization period 20 minutes without NTG. A venodilating dose of NTG (1 mcg/kg/min) was infused following preinduction hydration. Induction of anesthesia was with fentanyl (F) 50 mcg/kg, and a combination of 0.05 mg/kg of pancuronium and 0.05 mg/kg vecuronium.

Results. There was no significant difference in baseline hemodynamic measurements. After NTG was administered, the mean arterial pressure, PCWP, and LVEDD were significantly less in the 2 ml/kg volume administered group compared to the 12 ml/kg volume group. After fentanyl induction the 2 ml/kg group decreased MAP, LVEDD, and PCWP significantly from baseline and compared to the 12 ml/kg group.

Discussion. Our investigation shows a beneficial effect from 12 ml/kg preinduction volume infusion prior to narcotic induction. It maintains left ventricular end diastolic volume (LVEDV) and blood pressure following narcotic induction. Group 1 (2 ml/kg hydration) experienced a reduction in blood pressure during induction previously having responded with decreased LVEDV following a provocative low dose NTG test that unmasked decreased venous capacitance. Group 2 (12 ml/kg preinduction hydration) experienced increased LVEDV during NTG infusion and had stable blood pressure during induction. Relying on simple Swan-Ganz readings to predict a patient's fluid status may be erroneous at a time of high sympathetic tone prior to induction. Provocative testing with nitroglycerine may reveal a decreased PCWP in response to a dilated venous capacitance. This change correlates to a decreased LVEDD also found after NTG. Determination of LVEDV following a provocative NTG infusion is effective in predicting preload administration in cardiac surgical patients, maintaining hemodynamic stability during narcotic induction.

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LIMITATION OF PULMONARY VASODILATION EY NITROGLYCERINE SHOWN BY RIGHT VENTRICULAR

EJECTION FRACTION CATHETER

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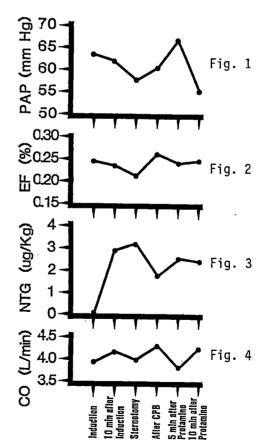
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Introduction. In patients who have high pulmonary artery pressures, the possibility of vasodilation and improvement of right ventricular (RV) function is desirable. Serial monitoring of RV function by thermodilution using a pulmonary artery catheter with a fast response thermistor and rapid calculation of RVEF has become feasible. Nitroglycerine, though not the most potent pulmonary vasodilator, is a safe choice in patients undergoing cardiac surgery. The results presented were gathered from 6 patients undergoing cardiac surgery who had an Edwards right ventricular ejection fraction (REF₁) catheter placed because of preoperatively raised pulmonary artery pressures. Institutional approval for retrospective analysis of data was granted. Five of the patients were for mitral valve replacement. One of whom had tricuspid and aortic valve replacement as well and one was for coronary artery bypass grafting.

A radial artery cannula, two 14 Methods. gauge IV and the REF. Edwards catheter were placed prior to induction. Induction of anesthesia consisted of fentanyl 25-40 ug/kg, vecuronium 10 mg, and pancuronium 1-3 mg. Maintenance was by infusion 0-5 ug/kg/min UD cardiopulmonary bypass (CPB). Nitroglycerine infusion (concentration 200 ug/ml) was given in increments of 10 ug/min until the pulmonary artery Hemodynamics were pressures started to decline. continuously recorded. At each incremental change of 20-30 ug/kg of nitroglycerine CO was measured in triplicate and the RVEF was computed by the RVEF computer. The rate of administration of nitroglycerine was compared to the PAP, REF, CO, and blood pressure. The same procedure was followed at induction, sternotomy, post bypass, and post-protamine administration.

Results. The REF and CO readings were variable out changed in the same direction and did correlate with reduction in the PAP. Nitroglycerine administration reduced the high pulmonary artery pressures in most cases though the reductions were not always remarkable. There was an optimal dosage of nitroglycerine which caused a reduction of PAP and rise of EF with a stable CO and blood pressure. Continued increasing dosage of NTG decreased EF, No, and blood pressure. Measurements are presented as simple means for each variable and plots of the important parameters in relation to the change are shown in figures 1, 2, 3, and 4.

Discussion. The measurement and nitroglycerine administration were performed at various stages of cardiac surgery and the events are not equally comparable. Before CPB the response of the PAP and EF to NTG were predictable. Post-CPB, however, the various actions of protamine varied the responses. Titration of nitroglycerine was in response to various high PA pressures and varied from patient to patient. The REF did prove useful in conjunction with normally recorded hemodynamic parameters, informing the anesthesiologist when the limit of improvement in REF had been reached. Increasing vasodilator therapy beyond a certain point caused a deteriorating blood pressure and CO and a decline in REF due to (a decrease in) both preload and afterload reduction.



ALPHAPRODINE : ITS PLACENTAL TRANSFER AND HEMODYNAMIC EFFECTS IN THE PREGNANT EWE

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Introduction. Alphaprodine (Nisentil) is a synthetic opiate agonist which has been used as an analgesics for 40 years. It was used extensively in obstetrical patients (1) until respiratory depression in mother and fetus were reported (2). However, alphaprodine administered during labor did not cause any adverse effects on the neonate (3). This study was undertaken to investigate 1.) the cardicvascular and respiratory effects of alphaprodine on mother and fetus in the sheep model 2.) placental transfer & pharmacokinetics.

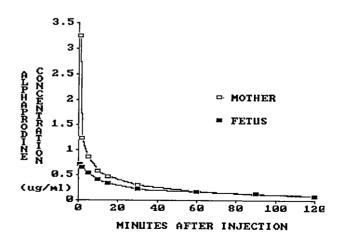
Methods. Eight pregnant ewes (40-50 kg) at 120-125 days gestation were instrumented with maternal femoral artery and vein catheters, a flow probe on the middle uterine artery, and a fetal carotid artery catheter. After 5 days recovery, the ewes received alphaprodine, 3 mg/kg, intravenously over 1 min. Maternal and fetal hemodynamics were monitored before and for 4 hours after drug administration. Uterine blood flow was measured continuously with a Dienco flowmeter. Arterial blood gases were drawn immediately before and 5, 10, 15 30, 45, 60, 120, 180, and 240 min after drug administration. At least 3 days after the hemodynamic study, placental transfer of alphaprodine (3 mg/kg) was determined in each sheep. Blood samples were drawn simultaneously from maternal femoral and fetal carotid artery catheters at before and 1, 2, 5, 10, 15, 30, 60, 90, 120, 180 and 240 min after drug injection. Blood levels were determined by gasliquid chromatography(4). Statistical analysis was done by analysis of variance for repeated measurements with Bonferroni t-test, accepting p< 0.05 as significant.

Results. Maternal HR increased to 26% above control 5 min after drug injection. There was no significant change thereafter. Maternal mean BP increased 16% at 5 min post-injection and remained significantly above control until 15 min after injection. Uterine blood flow decreased by 13% at 5 min. and remained significantly below control until 90 min post-injection. Fetal mean BP and HR increased by 14% and 5.9% respectively, at 5 min and there was no significant change thereafter. Maternal and fetal blood gases did not change signifi-cantly. Result of placental transfer was shown in the figure. The nighest blood levels of alphaprodine were found at 1 min after injection (maternal: 3.25 ± 0.63 ; fetal: $0.69 \pm 0.08 \text{ ug/ml}$). These levels fell below the sensitivity of assy (0.05 ug/ml) after 120 min. The fetal/maternal ratio was 0.21 at 1 min, 0.53 at 2 min post-injection and 0.9 at 5 min post-injection. It remained near unity thereafter. The results of pharmacokinetics will be published later.

<u>Discussion</u>. A large dose of alphaprodine was chosen for this study to facilitate measurement of maternal and fetal blood levels. This dose of alphaprodine caused a significant increase in maternal HR and BP, possibly secondary to the vagolytic effect of phenylpiperidine opiates. The increase in fetal HR and BP may also be explained by this mechanism since the drug readily crossed the placenta. The change in fetal hemodynamics was unlikely due to the small drop in uterine blood flow since the fetal blood gases did not reveal any compromise of fetal well-being.

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Title: HYPERGLYCEMIA IN THE PEDIATRIC PATIENT JBDERGOING HYPOTHERMIC CARDIOPULMONARY BYPASS

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Introduction. Hyperglycemia is a well recognized problem in the pediatric patient undergoing surgery, and is attributed to the stress of surgery itself. However, children undergoing cardiopulmonary bypass present a special problem, since deep hypothermia will abolish the insulin response to a glucose load and result in a failure to metabolize glucose.^{2,3} Therefore, not only is more glucose elaborated, but there is an inability to utilize it. It has been our observation that children are hyperglycemic in the postoperative period following cardiopulmonary bypass despite prolonged fasting and high metabolic demands. Glucose containing solutions are routinely infused intraoperatively to reduce protein catabolism during starvation and limit fat metabolism. Given our understanding of the effects of deep hypothermia on cellular metabolism, it is unclear if glucose infusions are warranted. We have assessed the significance of postoperative hyperglycemia and ascertained the amounts of intraoperative glucose received by children undergoing cardiopulmonary bypass at our institution

Methods. A retrospective review of 25 non-diabetic children undergoing cardiopulmonary bypass with deep hypothermia was performed. Institutional approval as obtained. The average age of the children was 3-1/2 years (3 weeks-13 years). Anesthetic technique and agents varied according to the anesthesiologist, with none of the children receiving high dose narcotics. Maintenance IV of D5LR were calculated based upon the child's weight and fluid deficit.4 Additional bolus IV fluids and blood products had been administered according to hemodynamic diameters and laboratory values for hematocrit, electrolytes and arterial blood gases. The total amount of fluids administered were recorded and from this the amount of glucose was calculated in mgm/kg/min that was received intraoperatively. Values for serum glucose were recorded for the following times: 1) preoperative baseline as a control, 2) in the immediate postoperative period upon arrival in the Pediatric Intensive Care Unit, and 3) the following morning of the first postoperative day at 6:00 a.m.

Results. A total of 25 charts were reviewed. The average duration of anesthesia was 6 hours, 20 minutes. The mean preoperative glucose of 91.1 mgm/dl was found to rise to 237 mgm/dl, with a range of 112-476 mgm/dl (p $\,$.005). The following morning the serum glucose was found to return to near normal preoperative values with a mean of 111 mgm/dl.

The total amount of glucose administered was found to be an average of 0.486 mgm/kg/min. The range of glucose administered spanned from 0.15 mgm/kg/min to 0.98 mgm/kg/min.

Discussion. Tolerance to prolonged starvation in children, as occurs in the perioperative period, is very limited. Firstly, they do not have the fat reserves that adults have for energy utilization. Secondly, the caloric requirements in young children are higher, with ranges of 80-140

kcal/kg/day described. Thirdly, the ability to utilize glucose as a non-protein energy source appears to be higher in children (probably because of smaller fat/energy stores). Recent work, using radio-isotope labeled glucose showed the direct amount glucose oxidized by the average adult to be 3-4 mgm/kg/min, while a premature infant utilizes up to 7 mgm/kg/min of glucose as the sole source of energy.⁵

Based upon the recommendation that approximately 80-140 kcal/kg/day (1.4 mg - 2.4 mg/kg/min) be provided to support metabolism and prevent ketosis, it is clear that we routinely administer glucose well below these suggested guidelines (mean 0.486 mgm glucose/kg/min). Despite receiving far less than prescribed, these children were still hyperglycemic postoperatively (Figure 1).

Previous evidence indicates that protein sparing is not achieved by intraoperative glucose infusion. Our data suggest that over wide ranges cf glucose infusions, there is no correlation with postoperative hyperglycemia and amount cf glucose infused. Future studies are needed to explore methods of increasing glucose utilization to control hyperglycemia intraoperatively, such as monitored insulin infusions, since regulation of glucose containing fluids appears to be ineffective at achieving this goal.

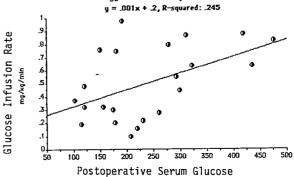
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Title: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION FOR LABOR ANALGESIA

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Introduction. The desire to have a natural, drug-free delivery has become increasingly popular during the last two decades. However, the majority of deliveries are supplemented with a variety of analgesic drugs and regional anesthetic techniques, none of which are totally risk-free. Transcutaneous electrical nerve stimulation (TENS) has been used to reduce pain by activating physiologic mechanisms which promote analgesia. The purpose of this study was to determine if TENS is effective in relieving the pain of labor and to evaluate maternal and fetal safety, and neonatal well-being.

Methods. We studied 89 unpremedicated healthy parturients at 37 to 42 weeks gestation who were in active labor with a vertex presentation and cervical dilatation of ≤ 5 cm. Patients with fetal distress, history of narcotic drug abuse, narcotic analgesia prior to entry into the study, previous use of TENS for pain relief, or significant medical problems were not studied. We obtained approval from the Committee on Human Research and informed consent. Patients were randomly assigned to one of three groups: functioning TENS device (TENZCARE®) (n=29); placebo TENS device (n=30); and a control group who received only conventional obstetric medications as needed (n=30). Patient selection was also control group who received blocked for parity. The patients were told that the use of the stimulator may not provide adequate analgesia and that conventional medications (narcotics, epidural analgesia) were available. Uterine activity, fetal heart rate, and fetal heart rate variability were monitored. The patient represented the intensity of pain by marking a visual analogue scale and the patient and the obstetric nurse assessed the patient's pain relief using a 5 point category rank scale. The condition of the infant was evaluated using Apgar scores, TSR, umbilical cord gas values, and the Neurologic and Adaptive Capacity Score at 0.25, 2, and 24 hours after birth. Data were analyzed using ANOV, chisquare, and the Fisher exact test. Values are presented as mean ± SE. A p value of <0.05 was considered statistically significant.

Results. Patients were comparable in age, height, weight, weeks of gestation, cervical dilatation at the time of entry in the study, and incidence of oxytocin augmentation of labor. There was no significant difference between groups in the percent of patients receiving epidural or narcotic analgesia for labor and delivery (figure). While more patients in the control primiparous group received intramuscular narcotics (8/15, mean 96.3mg ± 29.9 meperidine equivalent) than the primiparous group receiving the active TENS device (3/14, mean 41.7mg ± 10.1), this was not statistically significant. However, based on the patients' assessment, 93% of the patients using a functioning TENS device vs 62% of patients with the placebo TENS device achieved good to excellent pain relief during labor with the TENS device (P<0.C1). Based on the nurse's assessment, 81% (TENS) and 43% (placebo TENS) of patients had good to excellent analgesia (P<0.01). Of the patients who had the active TENS device, 93% said that they would use this again compared with 59% of patients in the placebo TENS group (P<0.01).

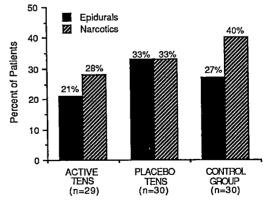
Electrical interference with the FHR monitor was a problem in one patient. Decreasing the amplitude or turning the device off allowed the FHR monitor to record a clean tracing. Review of the umbilical cord gas values, NACS, Apgar scores, and TSR revealed no significant differences between groups.

<u>Discussion</u>. Patients using a functioning TENS device had significantly more pain relief than those using a placebo device as judged by the category rank scale. The placebo effect, however, was greater than is commonly reported. While the differences in the use of narcotics was not significantly different, as has been previously reported², the data in the primiparous group suggested less use of narcotics and smaller doses when used. The electrical interference with the FHR monitor had no effect upon the fetus but could be a problem if there was any question concerning the fetal status and minute to minute observation of the FHR tracing was required. The TENS device would then have to be turned off and and the pain relief may be less effective without continuous stimulation. The use of the TENS device had no adverse effect upon the newborn. There was a high degree of maternal acceptance with this technique despite the lack of differences in more objective measures such as epidural and narcotic use. The use of TENS appears to provide some analgesia for labor, may decrease narcotic requirements, and be a useful alternative for analgesia during labor. It may prove to be a good first choice in patients seeking less intervention in labor and delivery.

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no significant difference between groups

Title: ISOVOLEMIC HEMODILUTION: A COMPARATITE STUDY OF DILUENTS

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Introduction. Preoperative hemodilution has regained interest since it minimizes the use of banked blood, reduces the risk of blood transmitted diseases as well as improving microcirculation at the tissue level. Attempting to determine the best diluent, we have compared the hemodynamic effects of using either a colloid or a crystalloid fluid as replacement of the blood removed.

Methods. Our study of transoperative hemodilution comprised 64 patients undergoing major elective operations with an estimated prediction of blood loss from 500 - 1500 mls. The following parameters were registered: EKG, heart rate (HR), mean arterial blood pressure (MABP), systolic (SBP) and diastolic (DBP) blood pressures, hemoglobin (Hb), hematocrit (Hct), bleeding profile and arterial blood gases. The volume of diluent, blood extracted and losses during surgery, were also registered. The hemodiluents were randomly assigned to each patient; 32 patients received Lactated Ringer's (L-R) and 32 others were given Dextran 40 (Dx40). After anesthetic induction using neuroleptoanalgesia, blood was drawn by gravity and simultaneously replaced with (Group I) L-R (in a proportion of 2:1) or Dx40 (Group II) (in a proportion of 1:1) (Table 1). The amount of blood to be drawn was calculated by the formula proposed by Bourke and Smith. The blood was kept in bags with an anticoagulant and mixed frequently. The patient's blood was retransfused soon after the phase of major blood loss was completed and hemodynamic parameters were then obtained before the end of surgery and again in the PAR area.

Results. The average amount of blood removed from Group I patients was $865(\pm 284)$ ml and for Group II $961(\pm 304)$ ml, over a period of 8-12 minutes. Most parameters studied, returned to normal after the reinfusion of the patient's own blood. Changes of Hct, MABP, HR, SBP and DBP were similar and without statistically significant differences in either group. However, CVP values at the end of the hemodilution (HMD), and 20 minutes later, were statistically significantly greater (p<0.01) in the L-R treated group. Of interest was the incidence of transoperative hypotension and postoperative pulmonary morbidity in the group of patients diluted with L-R (Table 2).

<u>Discussion</u>. Since in HMD, cardiac output compensatorily rises as blood viscosity and peripheral vascular resistance fall³, the selection of the hemodiluent is crucial. For these physiologic changes to happen before surgery, one must maintain a normal circulating volume. In this study, Dx40 seemed to cause less transoperative and postoperative morbidities. Colloids have the advantage of superior

intravascular retention resulting in a smaller volume requirement for HMD. On the other hand, because of greater extravascular redistribution, volumes of crystalloid used considerably exceeded the amount of blood removed. This difference may be the cause of the pulmonary complications noted in the postoperative phase. Be that as it may, preoperative hemodilution associated with reinfusion of autologous blood is an inexpensive and safe procedure, and also considered easy to perform while avoiding the dangers from diseases acquired by donated blood (i.e. AIDS, hepatitis, syphilis, Chagas' disease, etc.)

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TABLE 1. REMODILUTION STUDY OF DESTRAN 40 VS LACTATED RINGERS

	NO. OF	BLEEDING	EST. BLOOD	MEAN VOLUME	
	PATIENTS	(ml)	LOSS(ml) SURGICAL	OF DILUENT	
9x40	32	450-1450 ± 840	910 ± 486	950 ml ± 438	
L-R	32	520-1300 ± 780	820 ± 394	1800ml ± 372	

TABLE 2

TRANSOPERATIVE MORBIDITY			POSTOPERATIVE MORBIDITY		
DEXTRAN 40	Hct ∠ 25% 1	Hct ∠ 25% 1(3)		Hct ∠ 25% 1(1.6)	
L-R	Hct < 25%	3 (9)	Hct 25%	2(6)	
	Hypertension	1(3)	Hypertension	1(3)	
	Hypotension	1(3)	Atelectasis	2(6)	
	Tachycardia	1(3)	Pneumonia	1(3)	
			Thrombosis	2(6)	
			Pulmonary Edema	1(3)	

() Numbers in parenthesis represent percentages.

Title: HIGH-DOSE FENTANYL INDUCTION: THE EFFECT ON SPECTRAL EDGE FREQUENCY AND AMPLITUDE OF THE EEG Authors: MR Isley, PhD, ER Kafer, MD, BA Zech, BSc, EA Norfleet, MD, WJ Lucas, MD, DE Graham, BSc, and

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Introduction. Anesthetic induction is an extremely dynamic physiological event. The "induction effect", with any anesthetic drug, is most often described or evaluated by a number of cardiovascular anc respiratory variables. Since the major target orgar of anesthetic drugs is the brain, an adequate definition of induction with any anesthetic drug should also include cerebral function.

Interest in neurophysiological monitoring during anesthesia is as old as the history of EEG recording itself. Currently, computerized EEG analysis and display by on-line, commercially-available and user-friendly devices have provided two major advantages over conventional methods: 1) enhanced and transformed visual displays of the raw EEG for easy interpretation (Figure 1.), and 2) processing and storage of raw and computer-transformed EEG for further statistical processing (Figure 2.).

The purpose of this study was to describe quantitatively, using computer-processed EEG, the induction effect observed with high-dose opioid

anesthesia in cardiac patients.

Methods. All patients were ASA Class III - V (age: 29 - 70 yrs old; $\overline{x} = 57$) and institutionally-approved, individual informed consent was obtained (n = 12, CABG; n = 5, valve replacements). All patients were premedicated with diazepam (0.15 mg/kg orally), morphine sulfate (0.1 mg/kg, IM), and scopolamine (0.005 mg/kg, IM) 2 hours prior to anesthetic induction. Anesthetic induction and paralysis were achieved by $30 - 50 \mu g/kg$ of fentanyl, and 3 mg/ 14 mg of pancuronium/metocurine. respectively.

mg of pancuronium/metocurine, respectively.

Induction was assessed by changes in the EEG using the SRD Cerebro-Trac 2500 (Atede, Inc., Peekskill, NY). This brain monitor generated two channels of both trended and digital displays for: 1) "real-time" analog EEG (range, 0-30 Hz: amp, 0-200 µV) for the left and right cortical hemispheres, and 2) fast Fourier-transformed EEG displayed as a dot-density modulated spectral array (DSA) and spectral edge frequency (SEF, defined as the frequency below which 95% of the brain power is contained; Figure 1.). In addition, other physiological variables (e.g., frontalis EMG, HR, BP, SaO2, and PETCO2) were measured and displayed concurrently with the neural data in trended and digital format. Measurements for all cardiovascular and neural variables were taken before induction and immediately after induction but before intubation.

Results. For each cortical hemisphere, paired t-tests yielded highly significant results between the preinductior, premedicated baseline measures for SEF and EEG amplitude as compared with the immediate postinduction values. In particular, the SEF for each hemisphere was significantly decreased (preinduction: L = 21.9 Hz, R = 21.8 Hz; postinduction: L = 5.4 Hz, R = 5.2 Hz; for the L hemisphere, p < 0.00005, and for the R hemisphere, p < 0.00005) following induction, while EEG amplitude was significantly increased for each hemisphere (preinduction: L = 16.2 μ V, R = 15.6 μ V; postinduction: L = 31.7 μ V, R = 30.2 μ V; for the L hemisphere, p < 0.00005, and for the R hemisphere, p < 0.00005; Figure 2.).

Figure 1. shows this induction effect as reflected in a "snapshot" of the EEG and other trended physiological variables generated by the brain monitor.

Discussion. Neurophysiological monitoring during major surgery has become an essential element in the reportoire of the anesthesiologist. In particular, the EEG can be easily quantified and displayed by high-technology brain monitors for rapid on-line interpretation. For the first time, the anesthesiologist can "picture" the global physiological effects of anesthesia as the induction effect we describe here dramatically illustrates. In conclusion, the EEG changes with high-dose fentanyl were qualitatively characterized by a symmetrical: 1) decrease in SEF, 2) increase in amplitude and 3) development of a prominent delta band for the left and right cortical hemispheres.

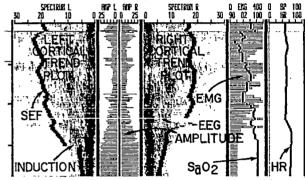


Figure 1. "Snapshot" of the induction effect generated by the brain monitor.

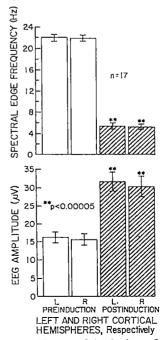


Figure 2. The effects of high-dose fentanyl on spectral edge frequency and amplitude of the EEG.

INTRATHECAL MORPHINE: EFFICACY, DURACION, OPTIMAL DOSE AND SIDE EFFECTS

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Introduction. There is a paucity of systematically documented information about the analgetic properties, optimum dose and adverse effects of intrathecal morphine, particularly in elderly and frail patients. Consequently we studied a range of doses and compared the analyetic and adverse effects with a controlled group of subjects who received no intradural opioid.

Methods. Thirty-three patients scheduled for total knee or hip replacement were included in this study after giving informed consent and institutional approval was obtained. They were divided into 4 groups - Morphine $0mg_*(n=10)$, 0.3mg (n=10), 1mg (n=10), and 2.5mg (n=3). The injectate was made up to a volume of 2.5ml with sterile water, and instilled intrathecally at the end of the surgical procedure. The subjects were randomly assigned to a treatment group and the drugs were administered in a double-blind manner. No premedication was given and systemic opioids were withheld until requested or deemed necessary in the postoperative period. Assessments were conducted by an investigator who was unaware of the constituents of the subarachnoid injection. They commenced 1 hour after the subarachnoid injection and continued for a minimum of 24 hours or longer until the effects of the morphine had receded. The observations comprised an analysis of pain and/or analgetic effect using a rank pain score system and numerical pain rating system out of 10. Adverse effects such as nausea, vomiting, urinary retention and reduction in respiratory rate (f) were sought. Repeated arterial blood gas measurements were done on 28 patients. Supplementary morphine analgesia was initially administered intravenously as requested and/or required by the patient. Thereafter intramuscular morphine was given. Statistical analyses were performed using the Kruskal-Wallis and Fisher exact probability tests.

Results. Intrathecal morphine provided profound, prolonged analgesia with all the doses tested. This was a significant improvement on the 0mg group (p<0.05) (Table 1). The 1mg and 2.5mg categories performed best. Although 0.3mg also provided good pain relief, it was unable to deliver prolonged analgesia in 3 patients (30%), who required supplementary analgesia 2.5-5 hours after the intrathecal injection. The median duration of analgesia was markedly increased following intradural morphine administration with all the doses used (p<0.05). The amount of additional morphine required in the 24 hours after the intrathecal injection was substantially less in the treatment categories than in the control group (0mg) (p<0.05). Clinically apparent respiratory depression (f<10) and $PaCO_2 > 50 mmHg$ were common

After apnea occurred in 3 patients, their sealed envelopes, containing the morphine dose information, were opened. It was discovered that, in each subject, 2.5mg had been given. Consequently this dose was discontinued.

after 1mg and 2.5mg, with the latter dose causing severe ventilatory inhibition requiring high dose naloxone therapy in 3 consecutive cases. Pruritus and urinary retention were frequently encountered. The incidence of nausea and vomiting was high in all groups. The results of the time to supplemental analgesia (T-supplement), dose of supplementary morphine in the first 24 hours, and side effects are shown in Tables 2, 3, and 4.

Discussion. Low dose intrathecal morphine (0.3mg) was associated with inconsistent duration of analgesia and irritating side effects. Larger amounts (1mg and 2.5mg) provided excellent analgesia, but were accompanied by a high incidence of respiratory depression. The best dose probably lies between 0.3mg and 1mg, and should provide superior prolonged pain relief, free from adverse ventilatory effects. It would, however, be associated with irritating adverse effects.

Table 1. Intrathecal morphine. Median pain score (ecale 0 to 10)

	(scare o to	10).		
Hrs after	0mg	0.3mg	1mg	2.5mg
opioid in	jn=10	n=10	n=10	n=3
1	5	0	0	3
2	6	0	0	0
3	5	0	0	0
4	3	0	0	0
5	3	1	0	0
6	5	0	1	0
8	5	0	0	0
10	5.5	0	0.5	0
12	5	0	0	0
16	3.5	0.	0	0
20	3	2	1	0
Table 2.	T-supplement	(hours)		
	Omor	0 . 3mcr	1ma	2.5mg

Median 1.25 21.25

(1.25-2.5) (2.5-36) (23-32) (26-50) Range

Table 3. Supplementary morphine dose (mg) in first 24 hours 0mg 0.3mg 1mg 2.5mg Median 45 Range (10 - 96)(0-26)(0-10)(0)

Table 4. Adver	Table 4. Adverse effects						
	Omg	0.3mg	1mg	2.5mg			
Pruritus	0/10	9/10	10/10	1/3			
Nausea/							
Vomiting	6/10	5/10	10/10	2/3			
f<10 breaths							
per minute	0/10	1/10	6/10	_3/3			
PaCO ₂ >50mmHg	0/8	1/8	6/9	*3/3 *1/3			
Urináry							
Retention Re-							
quring Cath-							
_eterization	5/9	5/6	7/7	2/2			
Those subject		37	1	1			

These subjects were stimulated by verbal arousal and naloxone infusion.

ANESTHETIC MANAGEMENT OF WON-IMMERSION-ESWL: A RETROSPECTIVE ANALYSIS OF 587 CONSECUTIVE CASES Title:

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 $\begin{array}{c} Introduction. \ Immersion-extracorporeal-shock \\ wave \ \overline{lithotripsy} \ (I-ESWL) \ has \ disadvantages \ (1), \end{array}$ including compromise of cardiocirculatory and pulmonary function caused by immersion, limited access to the patient hampering CPR, and a fixed size of patient support that excludes small children and morbidly obese adults from treatment. We report first experiences with a lithotriptor that does not require immersion of the patient

 $\underline{\text{Methods.}}$ The Lithostar TM (Siemens, FRG) is a multifunctional urological table which utilizes a new mode of shock waves generated along with local coupling to the patient (2). It is in use at Mainz University Clinics since March 1986. Shock waves are generated electromagnetically and applied to the catient via a silicone coupling head. Shock waves may be triggered by respiration and/or by the Ek.G-R-Wave. Anesthetic management included local infiltration (LI), regional techniques (epicural block (EDB), subarachnoid block (SAB), secation (S) and general anesthesia (GA) along with monitoring of EKG, blood pressure (oscillometry) and SaO, (pulse oximetry). Charts were reviewed for patient data, anesthetic management and complications.

Results. From March to December 1986, 587 NI-ESWL procedures were performed in 528 patients (ASA I-IV). These included 121 upper and distal uretral stones and 16 children (age 2 - 12 y). Pre-ESWL endourological procedures were performed in 179 cases. GA was given in 10 %, EDB/SAB in 45 %/1 % and LI with or without S in 44 %. S was provided by narcotics alone (78 %) or in combination with a spasmolytic (13 %) or by other combinations. This usually provided sufficient analgesia for stone fragmentation but occasionally produced transient hypoxygenation. Intraoperative hypertension occured in 9 % (EDB) and 21 % (LI/S) and was treated with intravenous analgesics or an antihypertensive (urapidil). At a fixed rate of 100 shockwaves per minute, triggered by respiration, arrhythmias occured in 14 % of applications. Out of those, 6 % required initiation of R-wavetriggering. With this mode, arrhythmias were seen in only 2 patient.

Discussion. Non-Immersion-ESWL is more convenient, versatile and economic than conventional ESWL, with a similar rate of stone disintegration. Free access to the patient and avoidance of immersion effects (1) are major advantages The specific wave form of the Lithostar shock wave, combined with a reduced energy level, causes less pain, thus reducing the demand for anesthesia. While GA was given during the urologists' training period it is today limited to some smaller children or when contraindications to other techniques apply. Regional techniques are used when lithotripsy is accompanied by endo-urological procedures. The current standard is LI of an area 5 cm in diameter (mepivacaine 1 %, 10 - 20 ml) in combination with systemic analgesics. With the R-wave triggering mode the incidence of arrhythmias (0.3 %) is considerably lower than with conventional ESWL (5.6 %, 1).

<u>Conclusions.</u> We conclude that NI-ESWL requires little - or sometimes no - anesthesia and is associated with cardiovascular stability. From the anesthesiologists' view, this compares favourably with conventional ESWL.

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Title: NEUROMUSCULAR BLOCKADE IN CAD - WH LF DRUG TO CHOOSE?

A CONTROLLED STUDY IN CONDITIONED MUMHOUNDS

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Introduction: The usefulness of pancuronium in patients with coronary artery disease was recently questioned (1). Suggested alternatives include metocurine, RGH-4201 (duador), atracurium and vecuronium (1, 2, 3). We have investigated effects of neuromuscular blockade on the cardiovascular system under standardized conditions in a dog model.

Methods: Five "conditioned foxhounds" were anesthetized (pentothal/fentanyl inf./N₂0), instrumented (art.can./p.a.-cath.) and then given pancuronium 0.1 mg.kg (P), metocurine 0.3 mg.kg (M), atracurium 0.4 mg.kg (A), duador 0.4 mg.kg (D) and vecuronium 0.1 mg.kg (V) in randomized sequence. 2, 5, 10, 20 and 30 min after administration cardiovascular parameters were measured and compared to control: heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmocapillary wedge pressure (PCWP) and cardiac output (CO). From these were calculated: stroke volume (SV), peripheral vascular resistance (SVR) and pulmonary vascular resistance (PVR). Histamine levels were obtained at 2, 5 and 10 min. The data were analyzed using the BMDP program system. Significance was assumed with p \leq 0.05.

Results: Administration of P, D and M was followed by an increase in HR (P 5'; M 2'; D 2, 5, 10'). CVP/PCWP decreased after P (2, 5, 10, 20'/2, 5, 10'), M (2'/2, 10, 20'), D (10'/2'). PVR/SVR decreased after P (5, 10, 20'/5'), M (5, 10'/2, 5, 10'), D (5, 10'/2, 5, 10'), V (2'/2, 5') and A (5'/-). Histamine levels did not increase.

Discussion: Myocardial 0_2 consumption is related to \overline{HR} , preload and afterload. Indirect parameters of the latter include CVP/PCWP, MAP/MPAP and SVR/PVR. Whilst MAP and MPAP remained fairly constant with all relaxants, HR was unaffected only by V and A. CO increased after all drugs, except A. However, in the case of D this was due to a pronounced tachycardia ($r^2 = 0.8$) whilst the CO increase following V correlated with SV ($r^2 = 0.6$) and a decrease in SVR ($r^2 = 0.66$). With respect to myocardial 0, consumption, our results support the use of Vecuronium or Atracurium in patients with reduced coronary reserve. The administration of Duador cannot be advocatec.

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Title: ROLTINE PROBING OF THE CANINE MAMMARY ARTERY IMPAIRS ENDOTHELIUM-DEPENDENT VASODILATION AND

PROSTACYCLIN PRODUCTION

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Introduction. The internal mammary artery is commonly used for coronary artery bypass because of improved long-term patency. Decreased flow through this vessel during and hours postbypass, however, may cause an initial impairment of cardiac function (1). It is routine practice for many cardiac surgeons to probe internal mammary arteries to dilate them prior to engraftment. We investigated the effects of such probing on endothelium integrity, vasodilation due to endothelium-derived relaxing factor (EDRF) and to prostacyclin, and arterial prostacyclin production.

Methods. Mongrel dogs (n=4) were anesthetized with pentobarbital (5 mg/kg) and invasively monitored. A midsternal thoracotomy was performed, and one internal mammary artery with its pedicle was isolated using magnifying loupes, removed, and divided into two segments. One segment was gently probed two times using a 1.5 mm coronary artery probe in a manner identical to that done clinically. vessels were placed in Krebs buffer and, using a dissecting microscope, carefully cleaned of fat and adventitia and divided into three mm rings. The rings were then hung in water-jacketed tissue baths of 37°C Krebs' solution gassed with 95%0₂/5%CO₂ and connected to Grass FT-03 force transducers to measure isometric tension. Optimal resting tension was determined by preliminary length-tension experiments, and active tension was applied with an EC50 dose of phenylephrine. Dose-dependent relaxation responses to the endothelium-dependent vasodilators, methacholine $(10^{-5} \text{ tp } 10^{-5} \text{ M})$, calcium ionophore (A23187; $10^{-6} \text{ to } 10^{-6} \text{ M})$, and melittin (1, 2, and 3 µg/ml) were determined both before and after addition of indomethacin (28 μM) to the baths (used to block any portion of the relaxation due to prostacyclin). In some experiments, aliquots of bath fluid were removed before and after addition of A23187, and radioimmunoassayed for 6ketoPGF₁ stable breakdown product of prostacyclin). The correlation between endothelial integrity and relaxation response of probed vs unprobed vessels was assessed by scanning electron microscopy in selected rings. Data were analyzed by paired t-tests and are expessed as mean ± SEM.

Results. The relaxation responses to all drugs studied were significantly impaired in probed vs unprobed vessels both in the presence (p<0.01) and absence (p<0.01) of indomethacin (representative data

at maximal doses in table). Prostacyclin release (as measured by 6ketoPGF, production) was significantly impaired (p<.05) in probed vs unprobed vessels under both basal (1.59 \pm .19 poles/mg tissue vs 2.1 \pm .14 pmoles/mg tissue) and A23187 stimulated conditions (5.7 \pm 1.1 poles/mg tissue vs 16.2 \pm 4.5 pmoles/mg tissue). The degree of impairment of relaxation response correlated with endothelial cell damage as assessed by scanning electron microscopy. Scanning electron micrographs of segments revealed marked endothelial disruption in probed vs unprobed vessels.

Conclusions. We have demonstrated that routine probing of dog mammary arteries causes significant endothelial cell damage, decreases the ability of the vessel to release prostacyclin, and markedly impairs relaxation responses due to EDRF and prostacyclin. It is possible that these factors contribute to decreased coronary flow following coronary artery bypass surgery. These results suggest that the probing of internal mammary arteries prior to engraftment should be avoided and that these vessels must be handled with extreme care.

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PERCENT RELAXATION OF DOG IMA ± PROBING, ± INDOMETHACIN

PROBED UNPROBED	MELITTIN -INDO 17.8± 4.5 41.6±13.9	, 3 UG/ML +INDO 10.6±2.6 27.2±5.2
	METHACHO	LINE 10 ⁻⁶ M
	METHACHU	LINE IU M
	-INDO	+INDO
PROBED	30.6± 7.2	20.8± 4.5
UNPROBED	52.3±11.3	40.4±10.7
		•
	A23187 1	о ⁻⁶ м
	-INDO	+INDO
PROBED	22.1±12.4	16.2± 5.7
UNPROBED	47.2± 7.2	44.1± 4.7
	· · · · · · · · · · · · · · · · · · ·	

Title: MISLEADING ESOPHAGEAL DOPPLER CARDILC OUTPUT DURING EARLY HEMORRHAGE IN PIGS

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Introduction. Monitoring cardiac output on a continous basis is of inestimable value in the management of critically ill patients. The most commonly employed method of measuring cardiac output, the thermodilution technique, is intermittent and invasive. Doppler ultrasonography is a noninvasive alternative that has been shown to correlate well with thermodilution cardiac output. We studied the relationship between continous esophageal doppler cardiac output (DCO) and continous Fick cardiac output (FCO) during progressive decrease in cardiac output by hemorrhage in pigs.

Methods. In six anesthetized pigs, average weight 40 kg, an esophageal doppler probe (Accucom, Datascope, Parasmus, NJ) was positioned in the esophagus to obtain a maximum blood flow velocity signal from the descending thoracic aorta. Continous FCO measurements were obtained using fiberoptic catheters in the pulmonary and carotid arteries for the measurement of Svo. SaO, respectively. A gas exchange analyser measured oxygen consumption. 2An IBM PC processed data to provide continous FCO. Prior to starting hemorrhage the esophageal doppler was calibrated to the FCO. Recalibration was carried out either for a probe shift advisory or for obvious failure of DCO to track the progressive hypovolemia. The animals were bled via a femoral artery line at a steady rate until death (approximately 45 minutes) for a total blood loss of about 1.5L or 40% of blood volume. Fick and esophageal cardiac outputs were recorded every minute and the data analyzed using least squares regression and correlation methods.

Results. A total of 340 simultaneous measurements of doppler and fick cardiac output were obtained from six pigs. In each pig it was necessary to recalibrate DCO after 200 to 500 ml blood loss, therefore the results before and after the recalibration were analyzed separately. In one animal (#5) it was impossible to obtain an adequate doppler signal before 250 ml blood loss, necessitating its exclusion from the prerecalibration analysis. The correlation coefficent, slope and intercept were obtained for each animal. The individual regression lines with pooled means and standard deviations for the two periods are shown in Figures 1 and 2.

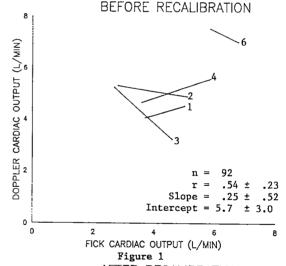
<u>Discussion</u>. The equation used by the doppler method is DCO = SVI x CSA x HR (where SVI = systolic velocity integral, CSA = cross sectional area of descending thoracic aorta, and HR = heart rate). The implicit assumption in this method is that CSA remains constant. The results suggest that during early hemorrhage this assumption is erroneous. Sympathetic activity associated with hemorrhage results in an increase in HR and SVI. The difference between the FCO and DCO during the initial bleeding period can be explained by a decrease in the CSA. The increase in SVI was probably responsible for the inappropriate probe

shift advisories of this version of Accucom. After recalibration, which was in effect resetting the CSA, the DCO tracked the FCO, suggesting a maximal decrease in the CSA.

We found the esophageal cardiac output monitor reliably tracked cardiac output only after the early period of blood loss.

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Title: THE INHIBITORY EFFECT OF METOCLOPRAMIDE ON PLASMA CHOLINESTERASE ACTIVITY

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Introduction: Metoclopramide is one of the most commonly used drugs in the perioperative period today. Metoclopramide is especially used by anesthesiologists as an antiemetic and to facilitate the gastric emptying and thus in the prevention of pulmonary aspiration of gastric contents in the preoperative period (1). Metoclopramide is also used frequently in the preoperative period by radiologists to aid in radiological examination of the stomach and small intestine.

Recently we observed prolongation of neuromuscular blcckade caused by succinylcholine in 5 patients receiving metoclopramide preoperatively. The chemical structure of metoclopramide is very similar to that of procainamide (2). We have previously demonstrated the inhibitory effect of procainamide on PCHE activity. Like procainamide, if metoclopramide inhibits PCHE activity, this would provide a mechanism for the prolonged duration of succinylcholine in patients receiving metoclopramide. Therefore, we studied the effect of metoclopramide on PCHE activity.

Methods: With the prior approval of our Institutional Review Board for the Protection of Human Subjects, we included 10 healthy ASA physical status 1 and 2 patients (ages 25-40, both sexes). Informed consent was obtained from all patients. Ten ml of venous blood was drawn into a heparinized syringe from each patient. Plasma was immediately separated and used for cholinesterase assay. The effect of metoclopramide at concentrations of 0.05, 0.1, 0.5, 1.0, 2.5, and 5.0 µg/ml was also studied on PCHE activity in each sample of plasma. A kinetic method described by Zapf et al (3) was used in the determination of PCHE activity and dibucaine numbers (DN).

Results: Table 1 contains the results. All the samples had a normal DN. The concentration of netoclopramide required to inhibit 50% of PCHE activity (I₅₀) was found to be 0.8 µg/ml or 2.4 x 10⁻⁶ M, when PCEE activity was plotted against plasma netoclopramide concentration (Fig). Linear correlation was evident, as indicated by a correlation coefficient (R) of 0.99.

TABLE 1: Effect of metoclopramide (MCP) on plasma cholinesterase (PCHE) activity

cholinestera	se (PCHE) activity	
MCP	PCHE Activity	% Inhibition
μg/ml	unit/ml	
	Mean + S.D.	
0 (control)	0.86 + 0.02	
0.05	0.79 + 0.02*	10
0.10	0.69 + 0.04*	20
0.50	0.50 + 0.03*	42
1.00	0.39 + 0.02*	55
2.50	0.24 + 0.01*	73
5.00	0.15 T 0.01*	83

* p<0.01 when compared to control (Dunnett's test); n=12

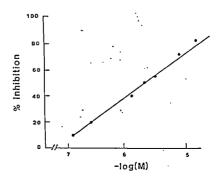
Discussion: Metoclopramide is increasingly being used by clinicians for the control of nausea and vomiting associated with narcotic analgesic therapy, radiation therapy, chemotherapy, pregnancy, and surgery and anesthesia (2). Metoclopramide in doses of 10-20 mgs is used by anesthesiologists to facilitate gastric emptying in the preoperative

A 10 mg dose gives a peak plasma concentration of up to 140 ng/ml (4). A dose of 1-3 mg/kg of metoclopramide has been used for chemotherapy induced nausea and vomiting, and doses up to 1000 mg per day have been tried as an antipsychotic agents. Peak plasma concentrations after administration of these high doses of metoclopramide have not been studied. We believe one should use caution when succinylcholine is administered in these patients especially in those who receive high doses of metoclopramide. PCHE is a mucoprotein produced mainly in the liver and is responsible for the metabolism of succinylcholine, a depolarizing muscle relaxant, and all of ester type local anesthetics. Metoclopramide has also been proven efficacious in the treatment of vomiting and reflux esophagitis associated with pregnancy (5,6). Since both pregnancy and the administration of metoclopramide are associated with a decrease in PCHE activity one should use caution when succinylcholine is administered in pregnant patients receiving metoclopramide.

In conclusion, our present study demonstrated that metoclopramide has a significant inhibitory effect on PCHE activity. Our data also showed that the concentration of metoclopramide required to inhibit 50% of PCHE activity (\mathbf{I}_{50}) was 0.8 µg/ml. We recommend that caution be exercised by anesthesiologists when they use succinylcholine, especially in multiple doses or in a continuous drip form in patients receiving metoclopramide.

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Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University $\begin{tabular}{ll} \end{tabular} \label{table}$

Title: ESMOLOL AS AN ADJUNCT TO NITROFRUSSIDE FOR CONTROLLED HYPOTENSION IN ANESTHETIZED DOGS

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INTRODUCTION: Esmolol (ES) is an ultra-short ac ing beta-adrenergic antagonist (1). Long acting beta-blockers have previously been shown to reduce the dose of nitroprusside (NP) required to produce deliberate hypotension, however, continued Leta blocking effects may persist beyond the cessation of the NP infusion. When compared as a sole agent to NP post-operatively, ES hypotension was associeted with reduced cardiac output rather than reduced with reduced cardiac output rather than reduced the hypothesis that combining NP + ES will reduce blood pressure with few deleterious effects in an anesthetized canine model.

METHODS: 18 conditioned mongrel dogs of either sex. were anesthetized with enflurane (2.2-2.3% end tidal). Normothermia and normocarbia were maintained. tidal enflurane (EF), CO₂, and O₂ were measured by mass spectrometry. Lead II of the ECG and heart rate (HR) were recorded. Arterial and pulmonary artery catheters were placed for measurement of mean arterial pressure (MAP), central venous and pulmonary capillary wedge pressures (CVP, PCW), and for thermodilut on cardiac output (CO) in triplicate. A micromanometer tipped catheter was placed for left ventricular (LV) pressure measurement and derivation of LV dP/IT. Systemic vascular resistance (SVR), cardiac index (CI), and stroke work index (SWI) were calculated. Periodic plasma samples were analyzed for ES and catecholam ne levels by HPLC. After 45 min of stabilization on EF only, baseline (B) cardiovascular measurements and plasma samples were taken. Group I continued to received EF only with measurements repeated every 30 min. Groups II and III, to test ES and NP alone and together and to control for order of drug administration, underwent 5 consecutive 30 min measurement intervals: II = ES alone, drug off, NP alone, NP + E3*, drugs off; III = NP alone, drug off, ES alone, ES + NP*, drugs off. The ES loading dose was 500 ug/kg over 1 min, followed by an infusion of 300 ug/kg/m.n. The NP dose was titrated to achieve a 20% decrease in MAP, not to exceed 8 ug/kg/min. (* For the combined drug periods: in group II, the NP dose was maintained while ES was added; in group III, the prior NP dcse was added to the ES infusion.) Repeat measurements were made at 30 min of each period. Changes with time in each group were analyzed by analysis of variance for repeated measures with Bonferroni t-tess. Analysis of variance with weighted t-tests was used to evaluate intergroup differences at comparable times. A p value < 0.05 was considered statistically significant.

RESULTS: There were no differences among the groups for any variable at B. In group I (EF alone) the ony changes with time were a gradual decrease in LV dP/dt CI, and SWI, and an increase in SVR. Results for groups II and III for B, 30 min of the drugs, and at 50 min of recovery (R) are shown in the figure. Asterises denote significant differences from gp. I (not shown n the fig.) at the comparable time. Mean ES levels were equivalent among the various ES administration periods in groups II and III (3.2-4.0 Ag/ml); ES was undetectable 30 min after ES infusion. At the time of the drug combinations, MAP, SVR, SWI, and LV dP/dt for NP + ES (gp. II) were equivalent to ES + NP (gp. III), and both were less than gp. I. CI for the

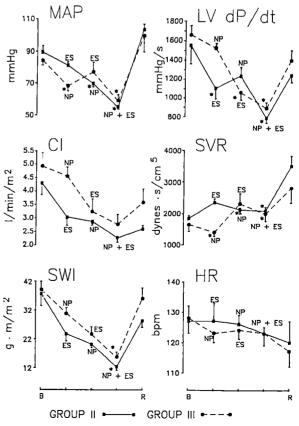
combined drugs was equivalent to CI with EF alone at the same time. HR was unchanged. PCW at B were 7-8 ± 1 mmHg among the groups; the only change during the drug infusions was a decrease to 5±1 mmHg with NP alone in gp. II. Plasma catecholamine levels were only increased with NP alone. At R, all variables were returned to levels equivalent to gp. I (EF alone) at the comparable time, with the exception of a higher post-drug PCW (10±1) in gp. III.

DISCUSSION: In an EF anesthestized canine model, ES was successfully used to augment the hypotensive effects of NP regardless of the order of administration, with reduced SWI, no increase in HR or plasma catecholamines, SVR lower than anesthetic alone, and no difference in CI from anesthetic alone. Recovery was prompt and complete for all of the variables studied. This drug combination may offer advantages in particular clinical situations when controlled hypotension is indicated.

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* = p < 0.05 COMPARED TO GROUP I

TITLE: THE EFFECTS OF INTRAVENOUS CIMETIDINE AND METOCLOPRAMIDE ON GASTRIC pH AND VOLUME IN OUTPATIENTS AUTHORS: R. Katende, FFARCS, I. Dimich, M.D., S. Michula, R.N., N. Sonnenklar, M.D. AFFILIATION: Department of Anesthesiology, Elmhurst Hospital, Elmhurst, N.Y. and Mount Sinai Medical Center, New York, N.Y.

Introduction:

Ambulatory surgical patients are at a higher risk of aspiration and regurgitation as they have higher volume of gastric juice and a lower pH compared to inpatients.[1]

The potentiation of the inhibitory action of Cimetidine (C) on H2 receptors by the simultaneous administration of anticholinergics has been reported.[2]

In this investigation, we evaluated the effect of Cimetidine alone, and the combination of Cimetidine and Metoclopramide (M) given parenterally, on the volume of gastric juice and pH in ambulatory patients undergoing elective surgery.

Methods:

The protocol was approved by the Institutional Review Committee and informed consent was obtained from all patients. Eighty (80) patients scheduled for laparoscopy or arthroscopy were randomly allocated into four groups with 20 patients in each group. Group I, outpatients, and Group II, inpatients, served as unpremedicated controls.Patients in Group II served as the basis for comparison with Group I outpatients. Group III, outpatients, received 300 mg cf C intravenously. Group IV, outpatients, received both C 300 mg and M 10 mg. Both drugs were administered, intravenously, 30-90 minutes prior to induction of anesthesia. Patients with gastrointestinal disorders, and obese patients were excluded from the study. No other premedications were given. After satisfactory induction of anesthesia (pentothal, succinylcholine) and endotracheal intubation, a #18F sump tube was passed into the stomach. Location was confirmed by insufflation and listening over the stomach. The patient was tilted head down and laterally to facilitate aspiration of gastric contents. The volume of the collected gastric juice was measured and pH determined by a technician unaware of the protocol. The pH of the gastric juice was measured by a Corning pH electrode. The incidence of nausea, vomiting, or other side effects postoperatively, were recorded. Statistical analysis using one way analysis of variance with Scheffs multiple comparison test. P values less than 0.05 were considered significant. Values are expressed as mean + SEM.

Results:

Patients in the control Groups I and II had a mean pH of 2.32 ± 1.23 and 2.78 ± 1.47 respectively. C increased gastric pH in Group III significantly, (p ≤ 0.05) to a mean 4.76 ± 1.54 . In Group IV, C and M further increased pH to 6.15 ± 0.71 (p ≤ 0.05). The four groups differed with respect to mean volume of gastric content. Mean gastric volume were 29.9, 23.6, 19.9, and 11.6 cc in Groups I to IV respectively, the proportion of patients

in the four groups with pH \leq 2.5 and volume \geq 25cc also were analyzed. The number of patients with the combination of both factors in Groups I to III were 9 (45%); 6 (30%); 1 (22%); respectively, and none in Group IV.

Three patients each in Group I and II, and two in Group III developed nausea and vomiting postoperatively.

Discussion:

This study confirmed clinical observation that outpatients are at a higher risk than inpatients are for developing acid aspiration.

Both regimens, C, alone and the combination of C and M were highly effective in increasing gastric pH and reducing gastric volume. However, it seems that effects of C and M were additive when administered together. None of the patients in Group IV had a pH \leq 2.5 or volume \geq 25cc.

Therefore, we recommend that outpatients receiving general anesthesia be given parenteral C and M preoperatively. In addition to providing greater protection against aspiration pneumonitis, this combination of therapy may also decrease the incidence of postoperative nausea and vomiting.

TABLE I

			No. of with p	Pts. H 4 2.5
Groups	<u>pH</u>	<u>Volume</u>	Vol.≯	
Group I Out-pt	2.33 ± 1.23	29.9 ± 15.9	No. 9	% 45
Group II In-pt.	2.78 ± 1.47	23.6 ± 13.97	6	30
Group III Out-Pt. C-300 mg	4.76 ± 1.59*	19.9 ± 15.21	1	5
Group IV Out-pt. C and M	6.15 ± 0.71*	11.6 ± 7.37**	0	0

* Compared to pH in Group I and II p < 0.05 ** Compared to Volume in Group I p < 0.05

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TITLE:

A COMPARISON OF COCAINE, LIDOCAINE VITH EPINEPHRINE AND

OXYMETAZOLINE FOR PREVENTION OF EPISTAXIS ON NASAL INTURATION

AUTHORS:

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Introduction. It is common practice to apply a vasoconstrictor to the nasal mucosa to prevent the epistaxis associated with nasotracheal intubation. Cocaine is usually considered the prototype drug for this purpose. If A number of studies have compared other agents to cocaine with equivocal results. This study examined the efficacy of the long acting adrenergic agonist oxymetazoline in comparison to cocaine and to lidocaine with epinephrine, a mixed alpha and beta adrenergic agonist.

Methods. Following approval of the Committee on Research Involving Human Subjects, and after having given informed consent, thirty-six patients over the age of sixteen undergoing oral or dental surgery necessitating nasctracheal intubation for general anesthesia were studied. The subjects were randomly assigned to one of three medication groups. Medications were supplied to the researchers by the pharmacy in a double-blinded fashion. Thirteen patients received 4% lidocaine with 1:100,000 epinephrine, thirteen patients received 10% cocaine and ten received 0.05% oxymetazoline. Medications were applied with cotton-tipped swabs for five minutes to both nares of the awake subjects. General anesthesia was induced ten minutes later with sodium thiopental 4-5 mg/kg I.V. Succinylcholine 1.5 mg/kg I.V. was given to facilitate tracheal intubation. A 6.5 or 7.0 mm i.d. nasal RAE tube for females and a 7.0 or 7.5 mm i.d. nasal RAE tube for males was passed through either the left or right naris after lubrication of the tube with surgilube jelly. The naris chosen was determined by each patient as that naris easier to breathe through. Where the patient could detect no difference, the right naris was always chosen. The tube was placed in the trachea under direct laryngoscopic visualization, with the aid of a McGill forceps. Epistaxis was then estimated at laryngoscopy according to the following scale: no bleeding - 0, blood only on endotracheal tube - 1, blood in pharynx - 2, blood in pharynx sufficient to impede intubation - 3.

Results. Results for each group, summarized in Table 1, were compared by Analysis of Variance. P<0.05 was considered to be statistically significant. The mean score for the thirteen patients in the lidocaine— with—epinephrine group was 1.08 \pm 0.852. The mean score for the patients in the cocaine group was 0.59 \pm 0.855 and the mean score for the patients in the oxymetazoline group was 0.3 \pm 0.675. Oxymetazoline proved to be more effective than lidocaine—with—epinephrine (P \leq 0.025). The difference in mean score between oxymetazoline and cocaine was not statistically significant (P \leq 0.375). Similarly, the difference between cocaine and lidocaine—with—epinephrine was not statistically significant (P \leq 0.375).

Discussion. Topical anesthesia of the nasal mucosa is one of the few remaining medical indications for cocaine. However, cocaine is a highly toxic agent whose effects may be manifested by excitement, anxiety, delirium and convulsions. Its sympathomimetic action may increase the likelihood of cardiac arrhythmias. Finally, it has a high potential for illicit use.

Lidocaine-with-epinephrine has a mixed alpha and beta sympathetic effect, and as expected, proved to be the least efficacious of the three medications at preventing epistaxis. We suggest that lidocaine-with-epinephrine be avoided in favor of a pure vasoconstrictor agent.

Oxymetazoline is a pure alpha-agonist. It does not inhibit the re-uptake of catecholamines, as does cocaine (and it has no effect on the myocardium. Perhaps most important, it has no mood-altering effect and therefore no potential for illicit use. It has fewer side-effects and is as effective as cocaine in preventing epistaxis following nasotracheal intubation. The availability of oxymetazoline offers yet another argument for the abolition of cocaine from the medical armamentarium.

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Table 1. Number of patients receiving score of 0,1,2,3 for each medication under investigation.

Score:	0	1	2	_3
Medication. Lidocaine with Epinephrine Cocaine Oxymetazoline	3	7	2	1
	7	3	3	0
	8	1	1	0

Title: ONSET, INTUBATION CONDITIONS AND DURATION OF ACTION OF VECURONIUM: HIGH DOSE VS. LOW DOSE

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Introduction. Vecuronium (VCB) is best known for its remarkable lack of cardiovascular side effects. However, as most other non-depolarizing muscle relaxants, its rate of onset, when given in doses one to three times its ED $_{95}$, is unable to provide a fast, reliable, optimal relaxation for endotracheal intubation. Although a few attempts had been made to use it as such², it is still unclear whether increasing the dose of vecuronium will result in faster onset times. In this study, we compared the onset time, duration of action and recovery pattern in patients given low dose 0.1 mg/kg (2xED $_{95}$) and high dose 0.4 mg/kg (8xED $_{95}$) VCR.

Methods. After Institutional Review Board approval, twenty four ASA I and II patients, ages 18-65 of either sex, excluding females of childbearing potential, were studied. Patients weighed less than 100 kgs., had no organ system disease, no known sensitivity to muscle relaxants and were undergoing elective surgery. Patients consisted of two groups: Group I patients were given 0.1 mg/kg of VCB and Group II patients 0.4 mg/kg. Heart rate and blood pressure (Dinamap) were recorded at regular intervals throughout the study. After supramaximal ulnar nerve stimulation, patient's neuromuscular function was assessed using both standard EMG recordings (NMT Puritan Benett) and adductor pollicis twitch monitoring. General anesthesia was induced after pre-oxygenation with thiopental 3-7 mg/kg and fentanyl 2-5 ug/kg. Maintenance was achieved with $N_20/0_2$ (60%/40%), enflurane (maximum end tidal concentration 0.5%), and additional doses of fentanyl (up to 10 ug/kg) as clinically required. Ventilation was controlled in order to maintain a Pa_{CO2} within normal range. After stabilization of the neuromuscular recording technique, VCB was given as a rapid bolus into a proximal IV site of a rapid flowing IV. When required by surgery, 0.03 mg/kg increments of VCB were administered at T_1 25% spontaneous recovery Onset time was defined as time from injection to maximal T_1 depression (>95% blockade), clinical duration was defined as time from injection to spontaneous recovery T_1 25%, and recovery time was defined as time from spontaneous recovery from T_{10} to T_{25} . Intubation was performed after maximum t_1 depression and was scored according to the following criteria: 1 - excellent: jaw and cords well relaxed, no reaction; 2 - good: slight cough, jaw cords well relaxed; 3 - poor: cough or movement, cords slightly adducted; 4 - impossible: jaw and/or cords tightly closed. Analyzed cardiovascular data were collected: after induction prior to relaxant, and after relaxant prior to intubation. Results were analyzed by the two-sample Student t-test; p results less than 0.05 were considered statistically significant.

Results. The mean values and the standard error of the mean for onset time, duration, recovery, and hemodynamic values are presented in table 1.

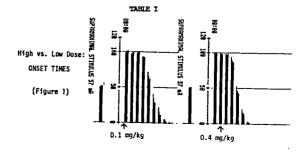
Increasing the dose of VCB from 0.1 mg/kg to 0.4mg/kg resulted in significantly shorter onset times (mean: from 198 to 94 seconds). When increasing the dose four times, the duration also increased approximately four times. However, 0.4 mg/kg VCB is associated with a much greater variability in duration (range: 60-215 mins.) than doses 0.1 mg/kg (range: 22-43 mins.). There was no significant difference in the mean arterial pressure and heart rate after relaxant in either group, nor in the rate of spontaneous recovery. One hundred percent T_1 depression was achieved in all patients. There was no evidence of flushing or EKG changes in the patients studied. Intubation conditions were "excellent" in most patients except three patients in group I where they were "good". Reversal of the neuromuscular block was easily accomplished in both groups when initiated at or above T_{25} recovery. There was no evidence of recurarization in either group. Figure 1 demonstrates the different onset times of the two groups.

<u>Discussion</u>. Vecuronium can safely be administered to patients in doses up to eight times ED_{95} , without additional side effects or significant changes in hemodynamics. Similar spontaneous recovery rates and patterns of reversal were observed in both high dose and low dose groups. The clinical properties of high dose VCB (0.4 mg/kg) may make this drug suitable for endotracheal intubation in prolonged surgical procedures.

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	n=12 0.1 mg/kg UCS	n=12 0.4mg/kg DCB		
Onset time (secs)	198.7 + 16.9	94.0 + 5.8 *		
Duration (mins)	32.2 + 1.7	121.5 + 14.6 +		
Spontaneous Recovery T10 - T25 (mins)	6.75 🛨 1.1	10.5 + 2.2		
Intubation Score	1.25	1.00		
MAP Prior Relayant	98.1 + 3.9	87.0 + 5.2		
MAP After Relaxant	93.1 + 4.4	81.1 ¥ 3.8		
HR Prior Relaxant	77.9 + 3.9	84.8 7 3.3		
HR After Relaxant	76.6 ± 3.75	82.7 ± 2.7		



TITLE: MAGNESIUM SULFATE ENHANCED RECOVERS OF IMPAIRED CEREBRAL BLOOD FLOW

AUTOREGULATION IN POSTASPHYXIC NEWBORN LAMBS

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Introduction Neonatal asphyxia impairs autoregulation of cerebral blood flow (CBF). In preterm neonates, loss of autoregulation allows C3? to vary directly with changes in arterial blood pressure and may result in intracranial hemorrhage. and central nervous system damage. Magnesium sulfate is widely used in management of parturients with preeclampsia. We have assessed the effects of a therapeutic level of magnesium sulfate on cerebrablood flow and its autoregulation after a period of asphyxia in newborn lambs.

Methods Eleven 1-3 day old lambs were anesthetised with 70% N2O, 30% O2, paralysed with d-tubocurarine and intubated and ventilated to maintain normoxia and normocarbia. Skin of groin and neck was anesthetised with 0.5% lidocaine for insertion of catheters into the femoral artery and vein and into the right lingual artery. 133Xenon was injected through the lingual artery and xenon washout from the brain was measured using a gamma counter. CBF was derived from the initial slope of the xenca washout curve. CBF autoregulation was assessed by determining C3F at resting, elevated, and decreased mean arterial blood pressures (MAP) before and after asphyxia. MAP was increased by infusion of 0.02% phenylephrine and decreased by infusion of 0.1% sodium nitroprusside solutions. After surgical preparation, the lambs were allowed to recover for two hours. After stabilization and demonstration of normal CBF autoregulation, 6 lambs received a load_ng dose of magnesium sulfate (80 mg/Kg) followed by a continuous infusion of magnesium sulfate at 48 mg/Kg/h until the completion of experiments. All Le lambs were subjected to 30 minutes of asphyxia (Parallis-32 mmHg, PaCO₂ 50-76 mmHg). After asphyxia, al lambs were maintained at normoxia and normocapnia cor the duration of the studies. Serum magnesium concentrations were measured with an atomic absorption spectrophotometer. Data were compared Fy analysis of variance and presented as mean ±SEM.

Results The CBF data are presented in the table. The serum magnesium concentrations of the treated lambs were 1.8 mEg/L before magnesium sulfabinfusion and remained in the range of 3.7 to 3.9 mEg/L during the studies. During asphyxia, CBF increased significantly in all the lambs. At 30 minutes after the end of asphyxia, all the lambs had increased CBF with MAP elevation and decreased CBF with MAP reduction. These changes indicate impairment of CBF autoregulation in all the lambs. At 90 minutes after the end of asphyxia, the magnesium sulfate treated lambs had recovered CBF autoregulation while the untreated lambs had persistent impairment of CBF.

<u>Discussion</u> These results confirm our previous studies which showed impairment of CBF autoregulation after asphyxial stress in newborn lambs. The magnesium sulfate treated lambs lost CBF autoregulation after asphyxia but made a significantly faster recovery than the untreated lambs. Our results are consistent with Altura and Altura's suggestions that prophylaxis with Mg²⁺ salts should be beneficial in brain ischemia.² Clinically, these findings indicate that magnesium sulfate therapy for parturients with preeclampsia, may not only be beneficial to the mothers but also to their neonates.

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CBF(ml/l00g/min)

	Untreated	Magnesium-
	lambs	treated lambs
Befcre asphyxia		
Decreased MAP	60 ± 3	54 ± 5
Resting MAP	63 ± 3	56 ± 5
Elevated MAP	63 ± 3	55 ± 5
During Asphyxia		
Resting MAP	206 ± 8**	147 ± 16**
30 min after asphyxia		
Decreased MAP	53 ± 3#	40 ± 2#
Resting MAP	61 ± 5	49 ± 3
Elevated MAP	73 ± 6##	63 ± 4#
90 min after asphyxia		
Decreased MAF	51 ± 3	43 ± 3
Resting MAP	52 ± 2*	44 ± 3
Elevated	58 ± 3#	48 ± 4

^{*} p<0.05; ** p<0.01 compared to CBF at resting MAP before asphyxia.

[#] p< 0.05; ## p< 0.01 compared to CBF at resting MAP at the same time period.

ABSTRACTS ANESTH ANALG S113 1988;67:S1–S266

Title: SIGNOIDORECTAL METHOHEXITAL AS AN INDUCING AGENT FOR GENERAL ANESTHESIA IN CHILDREN

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Introduction. Rectal methohexital had been used as a premedicant agent in children with variable success (1). When 25 mg/kg of 10% solution was used rectally, only 84% of the children fell asleep within 15 minutes. The mean time to the onset of sleep was 8.3±3.6 mins. A wide variation in the plasma concentration of the methohexital was found. Also, the incidence of premedication related defecation was 15%. The administration of 10% solution of rectal methohexital in mice is associated with inflammation, hemorrhage and ulceration of the rectal mucosa (2). Thus, a more dilute solution than the 10% may be preferred. 25 mg/kg of the 2% solution of rectal methohexital has been compared to the 10% solution (3). The 2% was associated with a higher plasma level of methohexital without affecting the speed or reliability of induction or the incidence of soiling. We studied the effect of further diluting the methohex tal to 1%. Therefore, using a larger volume may be more effective, thereby allowing lower dosages. Alour solutions were placed in the sigmoid area which may improve absorption and decrease the incidence of soiling. The influence of aspirating residual methohexital on recovery time was also studied.

Methods. .72 children, ASA I, with mean age 5.2 ± 1.4 years and weight 20.3 ± 6.3 kg, scheduled for ton-sillectomy and/or adenoidectomy and ear tubes were studied. Institutional approval and parents' informed consents were obtained. All the children were unpremedicated and accompanied by their families to the holding area. Every child was randomly assigned to one of eight groups.

Group	Conc.	<u>Dose</u>	Aspir.	Group	Conc.	Dose	Aspir.
1	2%	15mg	yes	5	1%	15mg	yes
2	2%	15mg	no	6	1%	15mg	no
3	2%	25mg	yes	7	1%	25mg	yes
4	2%	25mg	no	8	1%	25mg	nc
With t	he chil	dren 1	ying on	their s	ides an	d comf	orted
by the	parent	s, the	methohe	xital w	as admi	nister	ed via
				ion cath			
inches	rectal	ly and	kept in	place	until t	he ons	et cf
				s loss			
unresp	onsive	to ver	bal stin	ouli and	absenc	e of v	olur
				ated.			
				m resid			
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were m	onitore	d by a	n apical	. stethe	scope a	nd pul	se oxi-
				fall as			
				dequate			
then t	ranspor	ted to	the ope	rating	room an	d anes	thesia
was in	duced w	ith ni	trous ox	ide and	haloth	ane in	oxy-
				n was f			
							trolled.
				childre			
when t	hey reg	ained 1	their re	flexes.	Both	induct	ion
sleep	time an	d recov	very tiπ	e [from	end of	anest	nesia
till t	he chil	d reacl	nes a so	ore of	6 using	Stewa	rd's
post-a	nesthes	ia reco	overy so	oring s	ystem (4)] we:	re
record	ed. 3	factor	analysi	s of va	riance	was us	ed to
				the 3		were	lose,
concen	tration	, and e	effect o	f aspira	ation.		

Results. The mean sleep induction time following $25 \text{ mg/kg was } 6.0 \pm 1.7 \text{ mins which was significantly}$

shorter (p>0.0002) than when using 15 mg/kg (7.8±1.8). The sleep induction time using 1% solution was 5.9±1.3 which was significantly shorter (p>0.0005) than using 2% (7.5±2.3). The recovery time was significantly prolonged (p>0.0369) with 25 mg/kg as compared to 15 mg/kg. Aspiration had no significant effect on recovery time although we got 47±18% out of the administered volume. All the patients who received 25 mg/kg of the 1% solution (n=17) went to sleep within 15 mins. Only one patient out of 16 who received 25 mg/kg of the 2% solution did not sleep within 15 mins. Of the groups who received 15 mg/kg, 13 out of 30 patients (43%) did not go to sleep within 15 mins; 7 of them had 2% solution and 6 had 1% solution. 3% of the patients defecated.

Discussion. Rectal methohexital is a reliable technique to induce anesthesia in children. The success rate depends on both the dose and the concentration of the solution. When using a more dilute solution, a larger volume will be needed, thus a larger surface area of sigmoidorectal mucosa will be exposed to the solution, which improves absorption. In this study, using 25 mg/kg and 1% solution was associated with a faster induction of sleep and 100% success rate. In the previous studies, only 84% success rate was achieved when 25 mg/kg of 10% and 2%solutions of methohexital were placed rectally (1,3). As we placed the methohexital in the sigmoidorectal area, most of the solution will be transported to the portal system and exposed to hepatic first pass elimination. Thus, a higher dose will be needed. The low incidence of defecation in the study (3%) as compared to the previous studied, i.e. 15% (1), may be related to placing the methohexital in the sigmoid area instead of the low rectum.

In conclusion, 1% methohexital given in a dose of 25 mg/kg and placed in the sigmoid area appears superior to the use of 10% and 2% solutions and is associated with lower incidence of defecation. The aspiration did not affect recovery time.

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		n	Age	Weight	Sleep time	e Recovery
			(yrs)	(kg)	(mins)	time(mins)
Dose	15	19	5.2±2.0	20.6±7.0	7.8±11.8	35.5±17.0*
mg/kg	25	32	4.9±1.7	19.5±5.0	6.0±1.7∆	50.0±27.0
Conc.	1	27	4.6±1.8	18.0±5.4	5.9±1.3+	47.1±24.8
%	2	27	5.6±1.7	21.3±5.9	7.5±2.3	42.5±24.8
Aspir.		27				45.3±25.9
No aspir.		27				44.4±23.8
Δ p>0.00	002:		+ p>0.000	5: * n>0	0369	

DIAZEPAM-MORPHINE INTERACTION LY RATS: A NINE-FOLD INCREASE IN HYPNOTIC POTENCY

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Introduction. It is well known that opiates strengthen. the hypnotic effect of benzodiazepines in surgical patients (1,2). Although benzodiazepine and opioid receptors are pharmacologically separate, there are suggestions that these receptor systems may interact in the mediation of their effects (3). The aim of the present study was to investigate the interaction between morphine and diazepam regarding the hypnotic effect in rats.

 $\underline{\text{Method.}}$ Experiments were performed on 60 male Sprague-Dawley rats weighing 225-275g. The righting reflex test was regarded as positive if the rat failed to right itself within 15 sec after being placed on its side. The experiments were carried out in a clear chamber where oxygen was delivered. Each animal was given only one predetermined dose of an agent or a combination of agents. The agents or their combinations were injected into the saphenous vein over 30 sec in a 0.5 ml volume. Times between injections of agents and the righting reflex test were based on the times to peak effect of these agents: 15 min for morphine, 3 min for diazepam. With combined drug administration, both drugs were injected so that synchronization of the peak effect would occur. All experiments were carried out between 8:00 AM and 12 Noon. The interaction between the agents was determined in two steps. With the first step, three doseresponse curves (4) (three groups of experiments) were determined: two with the agents given alone, and the third group with a combination of the agents. Twenty animals were used to determine the dose-response curve for a drug or drug combination in each group of experiments with doses equally spread to give a range of doses that block the righting reflex in none or all of the animals in a subgroup. Diazepam dose range was from 2 mg·kg⁻¹ to 15 mg·kg⁻¹, and the morphine dose range was from 20 mg·kg⁻¹ to 40 mg·kg⁻¹. On the basis of the results obtained in the experiments where agents were given alone, their ${\rm ED}_{50}$ values were calculated to determine weight ratio between the components for the combined group of experiments. In the combined group of experiments the weight ratio between two components in all subgroups was 1:4.5 (diazepam/morphine) with the dose range from 0.1 mg·kg⁻¹ to 1.0 mg·kg⁻¹ for diazepam and 0.45 mg·kg⁻¹ to 4.5 mg·kg⁻¹ for morphine. With the second step, an algebraic fractional analysis of drug interaction at the ED₅₀ level (5) was used to determine the degree of diazepam-morphine synergism. The effect of diazepam-morphine combination on PaCO2 was studied separately in rats with arterial catheters implanted before the day of the experiment. Arterial blood gases were measured using an IL System 1301 Blood Gas Analyzer.

Results. The ED₅₀ level for diazepam was 7.6 (4.7-12.4) mg·kg⁻¹, and for morphine - 32.1 (27.0-38.1) mg·kg⁻¹. At the same time, the ED₅₀ level for diazepam-morphine combination was 0.4 (0.3-0.6) mg·kg⁻¹ (diazepam component) and 1.8 (1.2-2.6) mg·kg⁻¹ (morphine component). Comparison of the combined and single-drug ED50 doses (see table) shows that the sum of the fractional doses was nine-fold less than a single-drug fractional dose (0.11 vs 1.00, p<0.0001).

Discussion. Thus, interaction between diazepam and morphine in rats results in a nine-fold increase of hypnotic potency (combined vs single-drug). In surgical patients, naloxone (6 $\mu g \cdot kg^{-1}$, iv) has been found to antagonize the diazepam-induced anesthesia (6). This finding suggests that cpioid and benzodiazepine receptors are complimentary for hypnotic effect. Profound diazepammorphine synergism obtained in our experiments may be explained by the above assumption.

Table. Diazepam-Morphine Hypnotic Interaction

Fractional Equi-Effective Doses (ED50) of Diazepam-Morphine Combination

Groups	Diazepam Component	Morphine Component	Sum of Fractional Doses	Ratiob
D	1.00 (7.6) ^a	0.00	1.00	
D+M	0.05 (0.4)a	0.06 (1.8) ^a	0.11 p<0.0001	9.1
M	0.00	1.00 (32.1) ^a	1.00	-

D - diazepam group, D+M - combined diazepammorphine group, M - morphine group
- in mg·kg-1

- ratio of single-drug fractional dose to combined fractional dose

The p value denotes the significance of the difference between combined fractional dose and single-drug fractional dose.

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IS THE EFFECT OF SUCCINYLCHOLINE PREDICTABLE IN THE PRESENCE OF A NONDEPOLARIZING

NEUROMUSCULAR BLOCK?

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Introduction. Abdominal surgery occasionally requires a brief restoration of neuromuscular blockade to facilitate peritoneal and abdominal wall closure. Administration of succinylcholine (Sch) would appear to be ideal, but the combination of a depolarizing with a nondepolarizing muscle relaxant is both controversial and unpredictable. This study was undertaken to observe the effect of Sch when administered at various levels of recovery from an atracurium-induced neuromuscular block.

Methods. After approval of the study from the hospital research committee, 32 ASA class I or II patients undergoing elective surgery gave informed consent. They were randomly assigned to one of four study groups with eight patients in each. All patients received morphine (0.15 mg/kg) im one hour preoperatively and, after a defasciculating dose of atracurium (0.05 mg/kg) anesthesia was induced with sodium thiopental (3-7 mg/kg). Sch (1.5 mg/kg) was then administered to facilitate endotracheal intubation and anesthesia maintained with 0.7% isoflurane (end-tidal concentration) and 60% N₂0 in O₂. Neu-romuscular blockade was monitored using the integrated evoked electromyographic (IEEMG) response with the Datex Monitor. When the first twitch (T.) had fully recovered from the intubating dose of Sch. atracurium (0.15mg/kg) was administered to induce neuromuscular blockade. Spontaneous recovery of T. was observed at 20-s intervals until it had returned to one of four preassigned values. Patients in group I received 0.5 mg/kg of Sch when T, returned to 20% and those in groups II, III, and IV received the same dose when T_1 returned to 40, 60, or 80% of control respectively. The T_1 and train of four (T_1) response were observed at 20-s intervals for at least 3 min after the administration of Sch. The data were analyzed using the Chi-square test. A P value less than 0.05 was considered significant.

Results. In all patients in groups I and II, administration of Sch was followed by antagonism of the existing nondepolarizing block. In group III, Sch antagonised blockade in seven patients, and potentiated it in one. In group IV, potentiation occurred in six patients and antagonism in only two. These results are summarized in the table.

TABLE							
GROUP	I	II	III	IV*			
Antagonism	8	8	7	2			
Potentiation	0_	0	1	6			

*P < 0.05 (Group IV vs Groups I, II, and III)

Discussion. The precise mechanism of action of Sch in the presence of a nondepolarizing block is unknown. Sch may mimic acetylcholine (Ach) at the presynaptic receptor leading to increased mobilization and storage of Ach in the nerve terminal. Ach is then available in increased concentration to compete with atracurium at the postsynaptic receptor. Also, in the presence of a nondepolarizing block, Sch may compete with the atracurium for the postsynaptic receptor resulting in antagonism of the existing block. However, if a critical number of postsynaptic receptors are free, T > 80%, the effect of Sch on the postsynaptic receptor may predominate and induce a depolarizing block. study demonstrates that the effect of Sch, administered in the presence of a partial nondepolarizing block, is critically dependant on the level of block that exists at the time of administration. Neuromuscular blockade monitors currently used in clinical practice do not sufficiently quantitate the level of block to allow reliable prediction of the effect of Sch administered in this setting. The practice of administering Sch to facilitate abdominal closure in the presence of a partial nondepolarizing block cannot be recommended because antagonism of the existing block, rather than the desired effect, is more likely to occur if the precise depth of the block is not known.

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TITLE: DECREASING UNNECESSARY PREOPERATIVE TESTING IN PS I AND II PATIENTS.

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INTRODUCTION: Preoperative tests are frequently ordered by surgeons based on what they think the anesthesiologist requires to anesthetize the petient. This defensive approach may generate excess preoperative testing, particularly in healthy patients. To identify a minimum set of tests required for anesthesia care of ASA PS I and II patients, our day surgery unit (DSU) anesthesis staff developed a preoperative testing algorithm (Table). No similar algorithm was used for impatients (INFTs) at our institution. We used three approaches to determine whether the DSU algorithm was effective in reducing preoperative testing and whether any untoward perioperative events might have been avoided with additional tests.

METHODS: Study 1: For the first approach, we focused on differences in test use between similar groups of INPTs and DSU patients who underwent surgical arthroscopy of the knee or diagnostic laparoscopy. Data for this approach were from a study we conducted of resource utilization for INPT and DSU care. Study 2: To determine whether the DSU algorithm omits tests that might predict untoward events, we reviewed the records of alpatients admitted to the hospital following DSU care between January 1984-July 1986. Preoperative tests PS, surgical procedure and reason for admission were recorded, and the anesthesia, operating room and recovery room records were reviewed to determine whether the results of any preoperative tests would have suggested the likelihood of admission.

Study 3: To determine whether the algorithm might be appropriate for INPTs, we identified patient age preoperative tests, current medications, PS and untoward perioperative events from the records =1 all 1,015 elective orthopedic surgery INPTs discharged between July 1984-June 1985. The DEL algorithm was applied to this group of patients to determine the number of preoperative tests it would have generated and whether tests not indicated by the algorithm might have suggested the likelihood of any of the untoward events that occurred.

RESULTS: Study 1: Findings from the previous study indicated that a significantly greater proportion of INPTs undergoing each procedure had preoperative EKGs, chest X-rays and Panel 6 tests than did their DSU counterparts (p<.01 to p<.05). For example, \mathbb{Z}_{2}^{n} of DSU arthroscopy patients had a Panel 6 vs. 92% cf their INPT counterparts. Study 2: The most common reasons for the 100 PS I and II DSU patient admissions (out of 9,616 procedures) were vomiting, bleeding or pain. All cases of bleeding were due to extensive surgery. Two patients with abnormal preoperative EKGs were admitted to rule out myocardial infarction. Therefore, none of the 100 patient admissions would have been anticipated by tests other than those indicated by the algorithm. Study 3: 891 orthopedic INPTs (88%) were PS I or IL. Depending on the test, 41-96% of INPTs under 40 years of age (n= 503) had one or more tests no: required by the algorithm (e.g., 41% had EKGs, 69% had Panel 6s, 69% had PTs and 96% had UAs),

indicating that 2,357 "extra" tests were performed for this group alone.(Figure) At least 78% of PS I and II INPTs over 40 had one or more tests not indicated by the algorithm. Chart review for the 10% of patients with untoward perioperative events indicates that none of these events would have been articipated by tests not indicated by the algorithm.

DISCUSSION: A preoperative testing algorithm for PS I and II DSU patients produced far fewer preoperative tests for DSU patients than for comparable INPTs. Moreover, additional preoperative tests would not have suggested any of the 100 DSU patient admissions. Had the algorithm been used to determine testing of the 891 PS I and II orthopedic INPTs, at least 41% of preoperative tests may have been eliminated without contributing to untoward events. Specifying the preoperative tests necessary for anesthesia care in PS I and II patients may effectively and safely reduce unnecessary preoperative testing and its attendant costs.

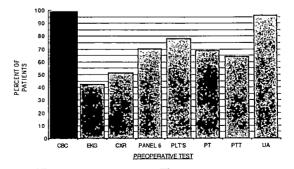
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Table:	n		
rapie:	Preoperative	Testing	Algorithm

		Ye	ars of As	e	antihypertensive
	under	40	40-59	60+	or diuretic use
CBC		yes	yes	yes	yes
EKC-		no	yes	yes	yes
Chest X-ray		no	no	yes	yes
Parel-6		no	no	ves	ves

FIGURE 1: PERCENT OF PATIENTS</br> RECEIVING EACH TEST



est indicated by algorithm it tests not indicated by algorithm

EFFECTS OF MYOCARDIAL INFARCTION ON HEMODYNAMIC RESPONSES TO VARIABLE DEGREES OF HEMODILUTION

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Introduction. We previously demonstrated that high degrees of hemodilution are not tolerated in the presence of severe myocardial depression. However, little is known about the effects of hemodilution in the presence of myocardial infarction (MI). This study was designed to evaluate the hemodynamic response to 25%, 38% and 50% reduction of hematocrit (Hct) in rats in the presence of significant MI (> 25%).

Materials and Study. Studies were performed on 58 male Sprague-Davley rats (body weight (BW) between 250-350 gm). After induction of MI using coronary artery ligation technique, these animals were subdivided into those who had developed MI and those in whom coronary ligation had failed to produce MI. Three to six weeks after coronary ligation, the rats received pentobarbital anesthesia (50 mcg/kg IP), were tracheotomized, and ventilated with room air. Arterial pressures were recorded from the right femoral artery; left ventricular pressures were obtained by a PE 50 tube passed to the ventricle via the right carotid artery. Following thoracotomy, electromagnetic flow meter probe was applied to the ascending aorta, allowing continuous recording of cardiac output (CO); 30 minutes after thoracotomy, hemodynamic indices were obtained as baseline prior to hemodilution. Isovolumic hemodilution was achieved with slowly withdrawing blood (1.7, 2.4 and 3% of rat's BW) from a femoral artery, and simultaneously replacing it with hetastarch solution in normal saline (Hespan) to reduce Hct by 25, 38 and 50%, respectively. Hemodynamic indices were measured after 15 minutes of stabilization. Acute volume expansion (40 ml/kg/min, for 45 sec) test was performed to determine peak CO and left ventricular end diastolic pressure (LVEDP) at which peak CO occurred. Peak stroke volume (SV) was calculated from CO and heart rate (HR) and peak cardiac index (CI) was calculated as CO divided by BW. At the end of the experiment the heart was arrested in diastole with potassium chloride. Passive pressure-volume relation was performed and ejection fraction index (EFI) was derived from SV and LV diastolic volume corresponding to LVEDP. The left ventricle was examined histologically to determine infarct size. Results. At lcw levels of hemodilution (25% and 38% reduction of Hot) in no MI, the reduction in total peripheral resistance index (TPRI) was associated with an appropriate increase in CI so that mean arterial pressure (MAP) was not significantly changed. However at 50% reduction of Hct, no MI group reduced MAP (-17%) despite apparent preservation of cardiac performance (EFI and peak CI). On the other hand, MI produced a reduction in cardiac performance even in absence of hemodilution (decreased EFI and decreased peak CI). At low level of hemodilution (25% reduction of Hct) in the group with MI, the increase in CI during hemodilution was restricted; however, MAP was still maintained as

compared to blood pressure levels in the MI group not subjected to hemodilution. At 38% and 50% reduction of Hct, MI group reduced MAP (-12 and -34%, respectively) in association with a decrease in cardiac performance (EFI and peak CI) indicating that the response of CI was inadequate for the reduction of TPRI. This alteration in cardiac performance at the 50% reduction of Hct was more marked in the MI group than in no MI group.

<u>Discussion</u>. Hemodilution was shown to have an inotropic effect, that is partly dependent on autonomic nervous system stimulation. This was true in our study, in hearts without MI when low levels of hemodilution were used. This effect was, however, not detected in MI hearts. The alteration in cardiac performance at all levels of hemodilution was more marked in MI than in no MI hearts, in particular at high levels of hemodilution. Thus, in both MI and no MI groups, the increase in CO secondary to hemodilution, was progressively restricted in relation to the degree of reduction of Hct so that, at high levels of hemodilution the reduction in TPRI mandated by local tissue needs was not compensated for, with a resultant decrease in MAP; these changes were more accentuated in the MI group.

In conclusion, impaired ventricular function may interfere significantly with the compensatory mechanisms induced by hemodilution. It seems plausible therefore to suggest that less hemodilution (< 38% reduction of Hct) be used in the presence of impaired cardiac function and that Hct values should be increased when hypotension is related to hemodilution.

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EFFECT OF MYOCARDIAL INFARCTION ON HEMODYNAMIC RESPONSE TO HEMODILUTION

		3% H		2,4%	2,4% H		H	No H	
		No MI	М	No MI	MI	No MI	MI	No MI	MI
Number in group		11	5	В	7	9	5	7	6
HR	В	409	410	422	426	434	406	425	384
ppm	Α	3900	375 0	397♦	3960	415♦	390♦	422	371
CI	В	192	185	214	207	176	184	193	160
m/min/kg	Α	2430	188☆	2580	230	2060	203	168	154
MAP	В	95	96	93	93	99	106	110	95
mmHg	Α	794	63 0 &	83	824	101	100	103	95
TPRI	В	0.47	0.55	0.45	0.48	0.60	0.60	0.60	0.61
mmHg/ml/min/kg	Α	0.320	0.340	0.340	0 384	0.50◆	0 52	0.57	0.61
LVEOP	В	2.7	5.3☆	24	50å	20	4.1	22	3.9
mmHg	Α	390	5.9	4.10	69	3.34	4.4	2.8	41
Peak CI mVmin/kg		340	257☆	366	280☆	347	312	327	2293
EFI %		76	36#	69	4311	64	42 x	66	32#

Values are mean. H - Hemoditution, B - before hemoditution, A - after hemoditution B vs A - ϕ - p < 0.05, ϕ - p < 0.01 MI vs No MI in the same hemoditution group - ϕ - p < 0.05, π - p < 0.01

Title: PAIN RELATED LATE EVOKED POTENTIAL COMPONENTS UNDER GENERAL ANESTHESIA

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Introduction: Intracutaneous electrical stimulation (IES) has been shown to elicitation related late cerebral potentials (EP) in healthy volunteers (1). The major use of evoked potentials in pain research has thus far focused on acute experimental 0.11 where the EP- amplitudes were shown to correlate with the painfulness of the stimulus (2) and to be reduced in a graded manner by opiate analgesics, aspiritation impramine (1). The aim of this study was to investigate if this holds true in getal anesthesia with halothane /nitrous oxide anesthesia in surgical patients.

Methods: After institutional approval and written informed consent had been obtained, EP due to IES were studied in 10 female patients free of CNS-acree drugs in the age of 38-57 years scheduled for elective surgery. In a prelimitery session before induction of anesthesia (without premedication) the indivi La sensation- and pain- thresholds were determined. EP were elicited by randomized stimuli of 2- to 3-fold pain threshold every 10 to 20 sec. Electroencephalogas (EEG) and electrooculogram recordings (bandpass: 0.5-30 Hz) were storecicn magnetic tape for off-line processing. EEG- and EP-recording sites were vertex-x-. linked earlobes. After digitization (100/s) EP were averaged over 40 stimuli withan analysis time of 1000 ms. Prestimulus EEG was processed by fast fourier transformation. Double recordings were performed the day before surgery and immediately before induction of anesthesia with etomidate (0.3 mg/kg body weilt) and vecuronium (0.08 mg/kg body weight). Patients were mechanically ventilated and PFTCO2 was held constant at 35-40 mmHg. Heart rate and blood press-ra (DinamapTM) were monitored continously.10-15 min after the start of nitrous oxds (FIO₂=0.3) and halothane (0.8-1.0 Vol%) admixture the first post-induc□ 1 stimulus block was started. After recording of at least two blocks (30-40 rip later) the admixture of nitrous oxide was terminated (FIO2=1) and recordings ware done under halothane anesthesia (0.8-1.0 Vol%) with the same and afterwards ☐th tenfold stimulus strength. Subsequently 0.25 mg Fentanyl i.v. was given. Averaged EP-amplitudes were subjected to statistical analysis by Dickson-Mood sign test == statistical significance was assumed at p < 0.05.

Results: Preinduction late EP components were comparable to those recorded in ¬·· laboratory in a population of healthy volunteers (1,2). Main components consisted C · · 1 vertex negativity at 130 ms (N130) and a positivity at 250 ms (P250) with a mear peak to peak amplitude of 20 μV. In the preinduction-EEG alpha activity w.is dominant. Induction and maintenance of an∋sthesia resulted in an increase of EE∋ power in both the low frequency (delta-, theta-band) and in the high frequency rame (beta1-band) during halothane/ nitrous oxide application. Late EP components wese abolished (amplitudes < 6μV) during halothane / nitrous oxide anesthesia. Lowerisc anesthetic depth by terminating nitrous oxice admixture did not reestablish late EEs but the 10-fold increase in stimulus intensity at this stage lead to reproducible EEs in the range of 100 - 400 ms with interindividual different shapes. Mean amplitude:

 $(\bar{x}=21~\mu V)$ were not significant different to control.These EP components could be suppressed again by application of 0.25 mg fentanyl.

Discussion: This study has been able to reproducibly record late cerebral EPs due to intracutaneous electrical stimulation during general anesthesia in the operating room. Such potentials have been demonstrated to be correlated to pain sensation in the laboratory in populations of young healthy volunteers (1). Corresponding to the anesthetic depth there was a change in the prestimulus EEG and in the late EP components. Additionally the results confirm the well known observation that halothane alone has no major analgesic potency. The recently developed method of intracutaneous electrical stimulation may thus open a new way of monitoring analgesia intraoperatively.

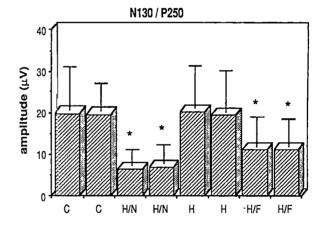


Figure 1: intraoperatively recorded amplitudes of EP-component N130/P250 (mean \pm SD) elicited by intracutaneous electrical stimulation (IES); C=control; H/N=halothane (1.0 Vol%) / nitrous oxide (FIO2 = 0.3); H = halothane (1.0 Vol%; FIO2 = 1); H / F = halothane (1.0 Vol%; FIO2 = 1) / fentanyl (0.25 mg). • p<0.05 vs control

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Title : FIRST PASS UPTAKE OF LIDOCAINE, DIAZEPAM AND THIOPENTAL IN THE HUMAN LUNG

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Introduction. In addition to exchange of gases, the lung has important non-respiratory functions such as uptake and metabolism of vasoactive compounds and exogenous drugs. Animal studies have suggested that the extent of pulmonary drug uptake is dependent on physicochemical properties of the drug with basic lipophilic amines exhibiting the highest lung tissue to blood concentration ratio. This uptake is rapid, extensive and occurs as a result of simple diffusion from blood in the lung. Limited studies in man have shown very high first pass uptake of lidocaine (60%), propranolol (75%), fentanyl (75%) and meperidine (60%). This study investigates the role of pulmonary drug uptake in man and the importance of the drug's physicochemical properties by comparing the first pass uptake of the lipophilic drugs lidocaine (L), diazepam (D), and thiopental (T).

Methods. Twenty-three ASA Class I-III subjects were studied prior to elective surgery. All studies were performed in accordance with and approved by the human studies committee and informed consent was obtained. In none of the patients was there evidence of lung disease. The patients were divided into three groups according to the drug studied. Radial artery cannula, CVP or Swan Ganz catheters were utilized for monitoring purposes, drug injections, and blood withdrawls. Preoperative medication was limited to morphine 4-10mg.

First pass uptake of L (30mg), D (10mg), or T (25mg) was determined using a multiple indicator dilution method with indocyanine green dye (ICG) 10 mg as the vascular indicator. After injection of a 2.0ml bolus of drug and dye into the CVP catheter, blood was withdrawn from the radial artery and collected in 1 sec. fractions. The blood ICG concentration with time was determined from absorbance at 805nm and blood concentration of L, D and T were determined by gas-liquid chronatography. Cardiac output (CO) was calculated from the area under the ICG curve and the % of injected drug taken up in the first pass by the lung was calculated from the difference in the area under the ICG and drug curves at the time when 95% of the ICG had passed through the lung.

		Body	Age	CO	78
Drug	N	Wt.(1b)	(Yr.)	(1/min)	uptake
Lidocaine	8	175+19	62.0+3.6	4.91+.34	60.5+7.4
Diazepam	8	182 + 16	59.9+3.5	6.11 + .78	33.8+3.7*
Thiopental	8	185 <u>+</u> 10	49.4 + 4.8	6.23 + .57	15.8+2.4*#

Significantly different from L at P < 0.01#Significantly different from D at P < 0.05

Results. The body weight, age, CO as well as drugs uptake are shown above. No significant differences in these parameters were observed between the three groups. There was no apparent correlation between CO and drug uptake. Figure 1 represents an example of first pass uptake curve in the human lung for lidocaine. Difference in the area under the ICG and L curves indicates 64.7% uptake of the drug for this patient. For all seven patients, uptake ranged from 36-81% with a mean +SE of 60.5+7.4% (above). The first pass uptake of D ranged from 16-46% of the injected dose with a mean+SE of 33.8+3.7% (above). Finally, the first pass uptake of T ranged from 7-24% with a mean+SE of 15.8+2.4% (above).

Discussion. The much greater uptake of L as compared to D and T could be explained on the basis of their differences in physicochemical properties. While all are lipophilic, L is a basic amine (pKa 7.9) whereas D.

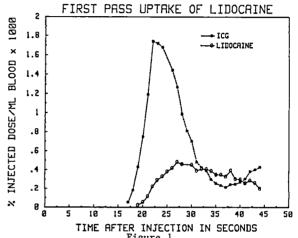


Figure 1 is an acidic compound. The uptake of D was significantly greater than T (P<.05) further suggesting the importance of an amine nitrogen in pulmonary uptake. Plasma protein binding may also be involved in the low uptake of D since minimal uptake was found in the isolated perfused rat lung (IPL) in the presence of albumin. However, omission of albumin from the artificial perfusate resulted in a ten fold increase in the uptake of D in the IPL⁴. It may be that the binding affinity of nonbasic drugs is much greater for plasma albumin than for lung structures whereas the reverse is true for basic lipophilic amines which bind primarily to acid glycoprotein.

An important aspect of the high first pass pulmonary uptake of L is the effect on its plasma pharmacokinetics. This early rapid pulmonary sequestration of the major fraction of an injected dose of L decreases the peak plasma level of L by several fold and moderates the rate at which it enters the systemic circulation. This may contribute significantly to the safety of lidocaine as well as other basic lipophilic amine drugs which show similar high first pass pulmonary uptake. Any situation which decreases this high first pass pulmonary uptake could expose other organs to much higher plasma concentrations of the drug. The presence of other basic lipophilic amines for example could compete with the first pass uptake of L. In addition, acute or chronic lung injury, manipulation by the anesthesiologist (one lung anesthesia), changes in lung perfusion (pulmonary embolism), or prolonged periods of cardiopulmonary bypass may decrease first pass lung uptake and increase peak plasma concentrations of the drugs in the blood entering the systemic circulation.

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EFFECTS OF HALOTHANE ON THE CONTRACTILE PROTEINS IN SKINNED MYOCARDIAL FIBERS OF NEWBORN TITLE:

AND ADULT RABBIT

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Clinical evidence suggests that re-Introduction. borns may be more susceptible to halothane-induced h tension than adults, and isolated cardiac muscle from newborn rabbits is more sensitive than that of adult racbits to halothane-induced depression of contractility. Thus, clinical hypotension in newborns is due at least in part to a direct action of halothane upon the myocardium. The mechanisms of action of halothane on newborn myocardium are undefined; one or more steps in the contractile process may be more sensitive to halothane depression in the newborn than adult heart. The purpose of this study was to compare the effect of halothane on Ca2+-activation of the contractile proteins in skinned myocardial c∈lis from newborn and adult rabbits.

Newborn (1-3 day-old) and young adult (2-Method.3 3kg) New Zealand white rabbits were sacrificed and the hearts were rapidly isolated. Right ventricular strip: were gently homogenized in relaxing solution (pCa>9) _h order to disrupt the sarcolemma. Fiber bundles (1-2 \mbox{nm} long, 100 µm wide, and 10-20 µm thick) were mounted in clips with one end attached to a photodiode tension transduce. Isometric tension was recorded with a Gould 2400S 4channel recorder. Newborn and adult preparations were studied simultaneously to assure identical conditions.

The bathing medium contained (in $\underline{m}\underline{M}$): $\underline{Mg^{2^+},1}$; $\underline{K}^+,35$: Na⁺,35; MgATP²,2; creatine phosphate²,15; EGTA,7; imidzzole; and propionate (major anion). [Ca²⁺] used were $<10^{-9}$ M (pCa>9), $10^{-5 \cdot 0}$ to $10^{-5 \cdot 6}$ M (pCa=5.0-5.6), arc 10^{-3.8}M (pCa=3.8). Ionic strength was 0.15, and pH 7.3 №1 0.02 at 20±2°C. Partial pressures of halothane (1,2 & 35) in experimental solutions were regulated with a Verni-Trol vaporizer using reagent grade N2 as the carrier gas.

Each fiber bundle was immersed in a series of control solutions (equilibrated with 100% N_2), then in a series of test solutions (equilibrated with N_2 plus halothane), and finally in control solutions again. Each such series of solutions alternated relaxing solution (pCa>9) with comtracting solutions (pCa=3.8-5.6); solution changes were made after steady-state tensions had been observed. Iscmetric tension development was measured for each contracting solution. The Ca^{2*} sensitivities of the preparations were determined by comparing the ratios of the tensor. developed at each pCa to the tension development at pCa-3.8. The effect of halothane on newborn and adult myocardial fibers was expressed as % of the mean of the THC bracketing control values. Data were converted to a nermal distribution with the arc-sine transformation prior to comparison using Student's t-test for paired and unpaired data. P<0.05 was regarded as statistically significant.

Results. Newborn myocardial fiber bundles exhibited a slight but significant increase in sensitivity to Ca^{-1} activation (leftward shift of the Ca^{2+} -activation curre) compared to adult fibers. The pCa's associated with 5C% of maximal contraction (pCaso) were 5.43 and 5.31 for newborn and adult, respectively (Fig. 1).

Halothane decreased the magnitude of maximal Ca-+activated tension (at pCa=3.8, Fig. 2) to a similar degres in newborn and adult myocardium. The effect was dos∈ dependent (slope=5.9% depression per % halothane).

Halothane also decreased adult submaximal Ca^{2^+} activated tension (at pCa=5.0-5.6), so that a rightward shift of the Ca²⁺-tension curve occurred at each concentration of halothane, but only at 3% halothane with newborn fibers (Fig. 3).

Halothane caused less depression of new-Discussion. born tham adult ${\rm Ca^{2}}^{+}$ -tension curves, but similar degrees of depression of maximal ${\rm Ca^{2}}^{+}$ -activated tension development. The greater sensitivity of skinned newborn myocardium to Ca²⁺ (Fig. 1) suggests a higher affinity of the (Fig. 1) suggests a higher affinity of the newborn regulatory proteins (troponin C) for Ca2 is consistent with the resistance of submaximal Ca2+activation of the newborn contractile proteins to halothane depression (Fig. 3).

Furthermore, the depression of maximal Ca2+-activated tension (Fig. 2) agrees with the inhibition by halothane of actomyosin ATPase, which could be due to depression of the number or strength of cross-bridge interactions. We conclude that the effect of halothane on the myocardial contractile proteins cannot account for the greater depression of newborn myocardial contractility observed in isolated intact preparations.² Additional mechanisms lead to the greater sensitivity of the newborn heart to halothane.

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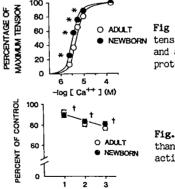
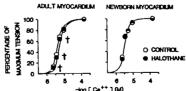


Fig 1. Ca²⁺-activated NEWBORN tension curves of newborn and adult contractile proteins.

Fig. 2. Effect of halo-thane on maximal Ca²⁺activated tension.



[HALOTHANE] (%)

Fig. 3. Effect of 2% halothane on the Ca²⁺-activated HALOTHANE tension curves.

p < 0.05 Adult vs. newborn p < 0.05 compared with control

Title: ANESTHESIA GAS DELIVERY SYSTEMS AND ANCILLARY MONITORS - A SURVEY OF IOWA HOSPITALS

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Introduction. Failure of anesthesia machines or inalequate monitoring of the gas delivery is a major cause of preventable mishaps during anesthesia. Various regulatory agencies have recommended standards for anesthesia equipment but no data is available on how the practice is followed in a community. This survey was conducted to evaluate the mechanical performance of anesthesia gas delivery systems (AGDS) and ancillary monitors in Iowa Hospitals.

Methods. The survey was conducted by the Iowa Department of Public Health (IDPH) in collaboration with the Department of Anesthesia, University of Iowa College of Medicine, under a contract from the Center for Devices and Radiological Health of the Food and Drug Administration (FDA). All hospitals in the State of Iowa were prorated according to their bed capacity and 45 hospitals out of 129 were randomly selected to represent the various sizes of hospitals. Voluntary participation was sought from the hopsitals by assuring them anonymity with the specific data throughout the project and during the final report. One hospital expressed concern regarding the release of information it considered proprietary and was replaced with another facility.

The survey consisted of a questionnaire and on site inspection of the AGDS. The questionnaire was sent to the Chief of Anesthesia and Administrator of participating hopsitals seeking information about the number of AGDS, number of years in service, maintenance history, modifications performed on machines since purchase, number of procedures performed per year using them, and the number of personnel involved in using AGDS. Once the questionnaire was returned, on site inspection of the anesthesia system was completed, according to guidelines prepared by us from recommended standards by various regulatory agencies and manufacturers. An approval of these guidelines was obtained from the Center for Devices and Radiological Health of Food and Drugs Administration. The on-site inspection of AGDS involved checking of piped and cylinders gases, inspection and accuracy of flow meters, placement and callibration of vaporizers, gas leaks in machines and examination and functioning of ventilators. Each AGDS was also inspected for presence and proper functioning of oxygen analyzers, ventilator rate and pressure alarms, oxygen/nitrous flow ratio alarm and oxygen pressure fail-safe mechanism. Liquid anesthetic samples were collected from 32 vaporizers and analyzed for any contaminents using gas chromatography interfaced to a mass spectrometer. Riken portable gas analyzer was used to measure accuracy of vaporizers. A written report of the inspection of each AGDS was provided to the hospitals and a copy of the final report was sent to each hospital at the conclusion of the survey.

Results. One hundred sixty-nine anesthesia machines were tested at 45 hospitals with anesthesia capabilities. These hospitals performed 67,243 procedures utilizing AGDS during 1985. The machines ranged in age from 1 to 28 years, with 47.3% manufactured since 1980, 39.1% between 1970-1980, and the remaining 13.6% prior to 1970, the oldest machine in operation was manufactured in 1958. Regular maintenance was provided for 112machines by the manufacturer while 55 machines were maintained by independent contractors. Two machines, designated as backup machines received no maintenance. There was no back-up supply of oxygen on five machines and 15 machines had leaks over 500 cc/min. Three hundred eighty-three vaporizers were examined, twenty of them were downstream to the common gas outlet. Fourteen vaporizers did not meet manufacturer's recommended calibration limits. None of 32 liquid anesthetic samples analyzed showed any contaminents. All flow meters and ventilators performed within the guidelines specified. A summary of ancillary monitors and alarms present and functioning on AGDS is shown in Table 1.

Summary of Monitors and Alarms

I	Device	% of machines with device	% working
Oxygen monito	or	75.1%	85.87
Ventilator ra	te monitor	19.5%	83.3%
Ventilator lo	w pressure alarm	87.0Z	97.2%
Ventilator hi	gh pressure alarm	25.2%	93.5%
Oxygen/nitrou	s flow ratio alarm	18.9%	1002
Oxygen pressu	re failsafe	100%	100 Z

Percentage based upon 123 machines equipped with a ventilator.

Discussion. There was no correlation between the age of the AGDS and number of malfunctions observed. We were surprised to find that 40% of the machines in active use lacked essential monitoring devices such as an oxygen analyzers and a ventilator/airway pressure alarm. ANSI, ASA and other regulatory agencies are working toward newer standards for anesthesia equipment and monitoring during anes thesia, it is evident from this survey that such recommendations or standards are poorly followed. It is our conclusion from this survey that a large number of AGDS without essential monitors are in service predominantly in rural hospitals of Iowa. Most of the anesthesia providers in these small hospitals have no decision making authority in updating or replacing antiquated equipment.

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Title:

COMPARISON OF ALFENTANIL AND SUFENT NIL IN THE AMBULATORY SURGERY PROCEDURE WHEN USED IN

BALANCED ANESTHESIA TECHNIQUE

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Introduction. An ideal anesthetic technique in the outpatient setting should provide adequate anesthesia, stable cardiopulmonary function, and uneventful recovery. Recently, several agents have been proposed to provide such conditions. Alfentanil (A) has a pharmacokinetic profile that is highly suitable for outpatient procedures. Sufentanil (S), another short acting narcotic thirty to forty times more potent than A, has not been studied extensively for outpatient procedures. We compared the quality of anesthesia and recovery of outpatients undergoing laparoscopy using a balanced anesthesia technique with equianalgesic doses of A or S.

Methodology. Forty-five unpremedicated patients consented to participate in this institutionally approved randomized, double blind study. One ml of study drug contained either 500 mcg of A or 12.5 mcg of S. All patients received 0.625 mg of droperidol, 0.02 mg/kg of pancuronium, and either 20 mcg/kg of A or 0.5 mcg/kg of S. Then, thiopental, 4 mg/kg, and succinylcholine, 1.5 mg/kg, were given IV. All patients' tracheas were intubated and 70% N₂O and 30% O₂ were inhaled to maintain general anisthesia. Ventilation was adjusted to maintain end tidal CO₂ between 35 and 40 mmHg.

Supplemental drug injections equivalent to 7 mcg/kg of A or 0.17 mcg/kg of S were administered intraoperatively for signs of light anesthesia and/or if blood pressure and/or heart rate varied more than 20% from control values. If an adequate response was not observed, or reoccurred within 2-5 minutes, a second injection of the study drug was administered. Then, if the second injection was insufficient, isoflurane was administered. Muscle relaxation was maintained with a continuous infusion of succinylcholine 0.2%. At the end of the surgical procedure N₂0 was discontinued. Time to extubation, alertness; and discharge following a modified Aldrete scoring system for ambulatory surgery were evaluated. Side effects, such as nausea, vomiting, pain, sedation, and need for medication were recorded.

A one-way ANOVA test, Fischer's exact test and Kruskal-Wallis Rank Sum test were used for analysis of HR, BP, incidence of side effects and duration of recovery.

Results. Patients in both groups were similar with respect to demographic data. There were no significant differences in the amounts of pancuronium, succinylcholine, thiopental, and narcotic used for induction of general anesthesia. Patients in group A received more study drug than patients in group S: 3.2 ± 0.6 ml versus 2.7 ± 0.7 ml (p < 0.02). Isoflurane supplementation was administered to more patients who received A than S: 5 of 22 versus 1 of 19. However, this difference was not significant.

Blood pressure and heart rate were similar at all times and not significantly different from control values, except following tracheal intubation and extubation (p < 0.05). At the time of first surgical stimulation and skin incision BP and HR, although not significantly different from preoperative values in either group, were significantly higher in patients who received A than S (p < 0.015). Incidence and severity of postoperative pain, nausea, vomiting, sedation, and recollection were similar in both groups. Time to discharge was similar in both groups.

Discussion. Equianalgesic doses of A and S have different effects. Although the depth of anesthesia, based upon BP and HR, was satisfactory in both groups, patients in group A had significantly greater variation in BP and HR than patients in group S at the time of first surgical stimulation and skin incision. Patients who received A also required more reinjection of study drug and additional isoflurane. These results may be explained in part by the different pharmacokinetic profiles of A and S, and suggest that A may be associated with less hemodynamic changes if given as a continuous infusion. It also is possible that the dosages of A and S were not equianalgesic.

In conclusion, we found that S appeared to be a better analgesic, provided greater cardiovascular stability, and was easier to administer than A. Therefore, S may be the preferred narcotic adjunct during balanced anesthesia for short surgical procedures, especially in an outpatient setting.

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Pulse oximetry during open heart surgery.

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Introduction. Pulse oximeters are widely used for noninvasive monitoring of arterial hemoglobin oxygen saturation (SaO2) in the operating room (1). However most anesthesiologists turn off the pulse oximeter during cardiopulmonary bypass (CPB) either because "zero" values are displayed or there is a constant "low-signal output" alarm and it is believed that the SaO2 values are not accurate. We therefore studied the usefulness and accuracy of pulse oximetry during and immediately after (CPB). Methods. After approval by our Human Subject's Committees and informed consent from each patient, we studied 15 male patients scheduled for elective open-heart surgery. A 20-gauge nontapered Teflon cannula was inserted percutaneously into a radial artery. A pulmonary artery catheter was also inserted via the right internal jugular route. Arterial hemoglobin oxygen saturation (SaO2) was continuously monitored with two pulse oximeters: Nellcor (N-100) and Ohmeda (Biox III, software version H). Finger probes were placed on the index finger (Biox III) and the middle finger (N-100) on the same side as the arterial cannula. ECG, heart rate (HR), intraarterial pressure (IAP), pulmonary artery diastolic pressure (PaDP), central venous pressure (CVP), and \$aO2 were continuously recorded on an 8-channel strip chart recorder. The SaO2 values were compared with C0-oximeter (IL 282, Instrumentation Laboratories) %HbO2 values measured intermittently from arterial blood samples. SaO2 and %HbO2 were recorded every 10 minutes prior to CPB, 2 minutes after the start of CPB and then every 10 minutes, and beginning 2 minutes after the discontinuation of CPB and every 10 minutes thereafter. No corrections were made for HbCO or HbMet. Statistical analysis was performed using two-factor analysis of variance (ANOVA), paired t-test, and linear regression and correlation analysis.

Results. Before CPB, both pulse oximeters gave accurate readings in all cases when compared with CO-oximeter. The mean SaO2 for N-100 before CPB was 99.36±1.23 (SD), for B III 98.06±1.19, and %HbO2 from the CO-ox 98.37±1.28. The r for N-100 vs CO-oximeter values was 0.928 and B III vs C0-oximeter 0.924. During CPB (nonpulsatile perfusion) with a membrane oxygenator (Shiley), the N-100 pulse oximeter indicated "no-pulse", and 0 SaO2 in all patients (Table 1). The B III displayed a "low signal output" message, but the SaO2 values (mean 96.7±1.1) were accurate when compared with C0-oximete values (97.72±0.76) in all patients (Table 1, which shows only the first value of each period). The lowest SaO2 value with the B III during CPB was 92%. Immediately after CPB the N-100 gave "zero" readings in 8 patients but recovered within ten minutes. There was a small but significant difference between N-100 and CO-oximeter readings (p≤.0001), but not between B III and CO-oximeter values. After CPB, B III readings were 1-3% lower than corresponding readings from the N-100, while the r value of B III vs CO-oximeter was 0.824 and that for N-100 to CO-oximeter was 0.783.

<u>Discussion.</u> Both pulse oximeters worked accurately before CPB. During and after CPB, if the oximeter gave readings, they were accurate when compared with CO-oximeter values and could provide useful noninvasive data. During and immediately after CPB some difficulties were encountered. Some of the difficulties during CPB could be related in part to hypothermia,

diminished distal blood flow, and the nonpulsatile mode of perfusion. The problems after CPB were not associated with diminished peripheral blood flow, because the SVR was low and the periphery warm due to use of sodium nitroprusside (SNP) or other vasodilating agents during CPB. It is known that SNP decreases forearm vascular resistance by 44% measured by plethysmography (2). It has also been suggested that venous dilation may cause venous pulsations and hence falsely low readings of pulse oximeters (3). The discrepancy between calculated, CO-oximeter, and pulse oximeter SaO2 readings may be explained by the compensation or lack thereof for HbCO and HbMet values.

Conclusion. The two pulse oximeters functioned accurately before CPB. However, during and immediately after CPB there were some disturbances. The extent of these disturbances seems to depend on the design of a particular pulse oximeter. The B III can be used throughout the operation during open heart surgery and provide accurate SaO2 values, at least within the limited range of this study.

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					TABLE 1				
	PRE -CPB			D	URING CP	В	AFTER CPB+		
Pariene I 2 3 4 5 6 7 8 9 10	N-1004 100 99 99 100 99 100 94 100 100 100	8-118 99 98 98 99 98 99 98 94 99 98 99	CO-Ox* 99 98.2 98.1 98.5 97.9 98.5 93 98.5 99.2 98.4 98.7 99.5	N-100 0 0 0 0 0 0 0	8-III 97 97 96 97 96 99 95 98	CO-Ox 98.2 98.0 97.5 97.0 97.1 97.0 98.5 96.5 97.6 97.0 98.7	N-100 100 100 0 0 0 0 0 0 0 0 0 0 0 0 0	8-III 97 99 98 94 97 97 dara 98 98 99	CO-Ox 96.6 98.0 96.5 98.2 98.0 98.0 98.0 98.0 98.9
13 14 15	100 99 100	99 97 99	99.3 98.2 99.5	0	97 98 96	98.1 99.0 97.2	100 0 100	100 96 99	98.4 98.2 98.7
	9=SaO2 1=%HbO2							inuces afa	

Title: LMW - HYDROXYETHYL STARCH AND RETICULOENDOTHE_MAL FUNCTION

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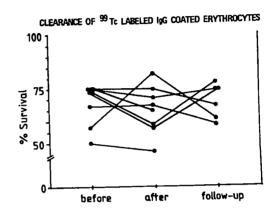
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Introduction. Among colloid solutions low molecular weight hydroxyethyl starch (LMW-HES, average MW=270000, hydroxyethyl molar substitution=0.5) appears to have a low incidence of side effects on the coaquiation system and therefore seems preferable to other solutions (1). However, a deleterious effect on the reticuloendothelial system (RES) function has been disputed to be induced by synthetic colloids rendering patients susceptible to bacterial infections. Previously, aggregated albumin, was used to assess RES function (2). However, disparity between immunospecific or receptorspecific clearance and particulate clearance is obvious (3). We therefore investigated the influence of LMW-HES on clearance mediated specifically by RES membrane receptors. Before and after hemodilution we measured splenic removal of Igcoated particulate complexes introduced into circulation in form of anti Rh_O(D) sensitized radiolabeled autologous erythrocytes.

Methods. 8 male patients (aged median $x_m=58 \, \text{years}$, range 46-63 years, all of them $Rh_0(D+)$), scheduled for vascular surgery, gave their informed consent to participate in the following investigation. No patient had a history known to be associated with immunoimpairment and all had normal liver and kidney function and no coagulation abnormality. 15ml/kg of body weight of blood was replaced by LMW-HES. Before and 24 hours after hemodilution prior to surgery and again several weeks thereafter clearance of autologous 99 Tc-labeled anti-Rh_o(D) coated red blood cells was measured. The 2.5 minutes value after injection was taken as the baseline (100% survival) with which the 45 minutes value was compared to calculate the percentage of erythrocytes removed from the circulation. Fach individual served as his own control. The same amount of IgG coating on rel cells in each subsequent experiment was ensured by a $^{125}\text{I-radioactive}$ antiglobulin test. Wilcoxon test for paired samples was used for statistical evaluation.

Results. Clearance of IgG coated red blood cells in the study group varied already before LMW-HES infusion (x_m =74.6% survival, range 50 - 75% figure). We noted no significant difference 2 hours after replacement with LMW-HES (x_m = 66.9% survival, range 45.6 - 82%; p>0.05). The follow-up study proved that each individual maintained the original anti-Rho red cell clearance value (x_m =71% survival, range 61.3 - 78%).

Hematocrit before blood replacement was 47±3%-thereafter 37±3% (p<0.01). Hemodilution and clearance investigations were well tolerated and without any side effects.



Discussion. Fc-specific splenic particulate clearance was not inhibited by LMW-HES. Thus, if at all, Fc-receptor inhibition by LMW-HES is short-lived. A single patient, however, had a weaker clearance after the infusion. Thus, an impairment of RES function cannot be ruled out in all subjects. The test proved to be individually reproducible since in all patients the sequestration pattern approximated the pretreatment level in the follow-up study. Several conclusions thus can be drawn:

- 1. In general, blood replacement with LMW-HES has no inhibitory effect on Fc-receptor mediated particulate clearance.
- 2. A considerable variation of test results is seen between individual surgical patients.
- Clearance of IgG coated erythrocytes remains constant in the individual patient and seems therefore a useful parameter in the perioperative period.

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Regional Cerebral Blood Flow During Nicardipine and Nitroprusside Induced Hypotension

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INTRODUCTION

Induced hypotension is frequently employed during neurovascular procedures to facilitate surgery and/or reduce blood loss. No ideal agent as yet exists for this purpose. Calciumchannel blockers are potent vasodilators which may reduce the incidence of postoperative vasospasm and/or offer brain protection. A new dihydropyridine derivative, nicardipine, is stable in intravenous form(1) and may be useful as a hypotensive agent. This study accordingly compares the regional distribution of cerebral blood flow and the corresponding change in the amplitude of the primary somatosensory cortical evoked potential (SSEP) during sodium nitroprusside-induced hypotension with that during nicardipine-induced hypotension.

METHODS

The experiment was approved by the Institutional Council on Animal Care. Twelve purebred beagle dogs of either sex with weights betwen 20 - 30 kg were studied. Anesthesia was first induced with Xylazine 20 mg IV and after transportation to the laboratory, supplemented with isoflurane. All animals were then intubated and mechanically ventilated to maintain end-tidal carbon dioxide between 35-40 mmHg. Anesthesia was maintained with isoflurane (end-tidal 1.3-1.4%) and pancuronium was given as needed. A femoral artery catheter was inserted for direct blood pressure monitoring and blood sampling. A left ventricular catheter was inserted via the other femoral artery for injection of radiolabelled microspheres. A triple lumen thermodilution catheter was also inserted for hemodynamic measurements. Arterial blood gas analysis was frequently performed to confirm the accuracy of the ETC02 and a Pa02 greater than 100 mmHg. Sodium bicarbonate was given when required to keep pH in the normal range.

Following insertion of catheters and stabilization of anesthesia, the animals randomly received either a nitroprusside infusion (0.01%) or a nicardipine infusion (0.02%). Regional cerebral blood flow (rCBF) was determined by injection of 15 μm microspheres labelled with Sc46, Ce141, Sr85 or Cr51. Brain samples from left and right parietal cortex, thalamus, medulla and pons were counted by gamma counter and converted to rCBF using a computer program.

Serial rCBF was measured four times: 1. Prior to the induction of hypotension 2. During hypotension at a mean pressure of about 40 mmHg. 3. Following return of normal blood pressure and 4. Elevation of the blood pressure to 20% above control pressure using an intravenous infusion of phenylephrine. All measurements were taken after at least 15 minutes of stable blood pressure. Hemodynamic monitoring including cardiac output(CO)by thermodilution was determined prior to the right or left parietal cortex using a skull screw in response to stimulation of the contralateral median nerve.

RESULTS

Two animals in the nicardipine group were excluded due to cardiac arrests following nicardipine infusion, and in one nicardipine dog the phenylephrine-induced hypertension part was omitted. The percentage change in flow with serial measurements for all four regions are displayed in the figure. There was no significant change in rCBF with sodium nitroprusside throughout the measurement periods whereas a

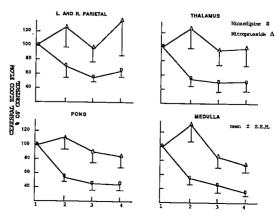
progressive reduction in rCBF was noted with nicardipine. (p <0.05 Dunnett's Test). In all four regions, rCBF was better maintained during sodium nitroprusside-induced hypotension compared to nicardipine-induced hypotension. This difference was highly significant for the thalamus, medulla and pons (p <0.01 two-way analysis of variance for repeated measures). The difference for the parietal regions was associated with p=0.06. There was no difference in CO between the groups. SSEP decreased during hypotension in the nicardipine group, but not in the nitroprusside group (p<0.05). Moreover, an average of 119 \pm 20 minutes was required before the blood pressure returned to normal following the hypotensive period in the nicardipine group. Only 33 \pm 7 minutes was required in the nitroprusside group (p<0.005).

DISCUSSION

Since calcium-channel blockers may reduce the incidence of postoperative vasospasm and have also been demonstrated to have a brain protective effect under some experimental conditions, they have theoretical advantages as hypotensive agents. However, in the present experiment the rCBF was poorly maintained compared to sodium nitroprusside. A 40 to 50% reduction in rCBF occurred with the onset of hypotension. This reduction in rCBF persisted despite return of the blood pressure to normal levels. The subsequent infusion of phenylephrine to raise the blood pressure to 20% above normal level also failed to have any effect on the rCBF. The findings of a reduction in rCBF in the somatosensory cortex is consistent with the reduction in SSEP amplitude in the nicardipine group. As CO was no different between the groups, a reduction in CO is not a factor contributing to the reduced rCBF. In summary, although nicardipine may be useful for control of hypertension(2), as an agent for induced hypotension it is associated with a significant reduction of rCBF which persists despite return of normal blood pressure. We therefore conclude that nicardipine is unsuitable for use as a hypotensive agent.

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TITLE:

DIRECTLY MEASURED UTERINE TOTIL AND BLOOD LOSS DURING ANESTHESIA FOR CESAREAN SECTION

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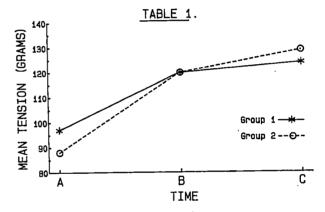
Dallas, Texas 75235-9068

Introduction: Blood loss following cesarean section (C/S] is often attributed to volatile agents used as part of a balanced emesthetic technique. In sufficient concentrations these agents are known to cause uterine relaxation. The possibility that the degree of uterine relaxation is directly related to operative b cod loss has not been proven. This study compares the effect of cifferent balanced anesthetic techniques on blood loss and uterine tone during C/S. We describe a direct measurement of tone previously unavailable using a method of indentation tonomity.

Methods: With approval of the Institutional Review Bcard, twenty ASA Class I-III gravida presenting for C/S under general anesthesia were randomly assigned into two groups. All received 30 ml of Bicitra® p.o. prior to rapid sequence induction with intravenous ketamine 1 mg . kg-1 and succinylcholine 1.5 mg . Fg-1. Endotracheal anesthesia was maintained with 50% N2O: 50% D2 until clamping of the umbilical cord. At this time patients in group I were given midazolam 2.5 mg IV and maintained on 7 ≥% N2O:30% O2. Patients in group II were given isoflurane to andtidal (E,) level 0.6-0.7% until cord clamping, and mainta med thereafter with E, 0.3-0.4%. These values were monitored by the in-line medical mass spectrometer. All gravida received oxytorin by infusion (20u . [1]) immediately after delivery and appropriate intravenous bolus doses of morphine (0.1-0.2 mg . kg-1 fentanyl (1.0-2.0 $\mu g \cdot kg^{-1}$) and atracurium (0.1-0.3 mg $\cdot kc^{-1}$). Using a modified applanation tonometer (UTHSCD) calibrated in grams, uterine indentation was measured after delivery of the fett s/ neonate (A), after placental delivery (B), and three minutes herer (C). Operative blood loss was estimated by the change in preand post-operative hematocrits. To assess the frequency of awareness and dreams, the patients were interviewed prior to discharge from the recovery room. Data were subjected to repeated measures analysis of variance and adjusted to significant levels using Bonferroni multiple comparisons procedure.

Results: Table 1 indicates the tonometer readings in grams at the different times. Uterine tone in both groups at time (A) was significantly different from the tone at time (B) and at time (C) (p = 0.0001). There was no significant difference with respect to uterine tone between Groups I and II, nor was there any difference between the groups in respect of blood loss. The average fall in hematocrit in Group I (mean value 30.7% after surgery) was 3.75% compared with the fall in group II (mean value 31.6% after surgery) of 4.31%. No correlation is shown at any time between uterine tone and the fall in hematocrit (p = 0.8 for group I and p = 0.7 for group II). None of the patients complained of awareness or dreams³.

<u>Discussion:</u> That tonometry does reflect the tone of the surgically-exposed uterus is seen in the consistent rise in indentation pressure as the uterus contracts in response to oxytocin. However, the quantitative values of tone at times of measurement could not be used to predict the amount of operative blood loss. The results further indicate that a balanced anesthetic technique with isoflurane, in the dose range described, and a vapor-free anesthetic are both associated with a similar blood loss for C/S, which is less than previously described⁴. We believe that the modified applanation tonometer is a valuable tool in quantifying the effect of uterine response to drug administration during C/S.



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Title:

CEREBRAL AND AFFERENT MUSCLE RESPONSES TO SUCCINYLCHOLINE IN DOGS PRETREATED WITH

PANCURONIUM

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<u>Introduction</u>. A previous report from our laboratory noted cerebral blood flow (CBF) increases following i.v. succinylcholine (SCh) in lightly anesthetized dogs (1). Subsequent studies (unpublished data) have demonstrated SCh-induced increases in afferent muscle activity (AMA) and support the hypothesis that CBF increases following SCh are primarily related to SCh-induced increases in AMA and secondarily related to SCh-induced $PaCO_2$ increases. The purpose of the present study was to evaluate the CBF, AMA, and PaCO2 responses to i.v. SCh in dogs pretreated with "defasciculating" doses of pancuronium.

Methods. Six dogs weighing 14.7 \pm 0.9 kg (mean + SE) were anesthetized with halothane, and the trachea was intubated without the use of muscle relaxants. Control PaCO $_2$ was maintained near 40 mmHg and PaO $_2$ was maintained near 150 mmHg. A femoral artery cannula was used to measure mean arterial blood pressure (MAP). Hemispheric CBF was measured by direct cannulation of the sagittal sinus (1). Brain and esophageal temperatures were maintained near 37°C. Afferent muscle activity from the right pelvic limb gastrocnemius muscle was recorded from a branch of the tibial nerve, and signals were quantitated using a saturating diode integrating circuit. The electromyogram (EMG) was recorded from the semitendenosus muscle of the same limb. For 20 min prior to control measurements and during the study period, dogs were maintained at 0.87% end-expired halothane (1.0 MAC), and ventilation was not further adjusted. After control measurements, three dogs received pancuronium 0.01 $\rm mg\cdot kg^{-1}$ and 5 min later SCh 1.0 $\rm mg\cdot kg^{-1}$ i.v., followed 45 min later by repeat control measurements and treatment with an equal volume of saline placebo. The remaining three dogs were given the same doses of pancuronium plus SCh and placebo; however, the sequence of relaxant and placebo treatments was reversed. Data following SCh and placebo treatments were expressed as a percent of their respective control values, and the percent of control values were compared using paired t-tests. A p value < 0.05 was considered significant.

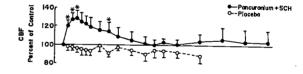
Results. There were no significant differences between cerebral and physiologic variables during the control periods before the administration of either SCh or placebo. There were also no significant differences in MAP following SCh versus placebo treatments. No dog had visible fasciculations following i.v. SCh, and only one dog had EMG evidence of fasciculations. Within 1 min after i.v. SCh, there were parallel increases in both AMA and CBF (Fig 1). The peak AMA value of $255 \pm 56\%$ of control occurred at the 1 min measurement period and was followed by a gradual decline in AMA; however, AMA following SCh was significantly greater than AMA following placebo during the consecutive 1 to 18 min measurement periods. Cerebral blood flow following i.v. SCh was significantly larger than post-placebo values during the periods of greatest AMA (i.e. the 1 to 3 min measurement periods) with peak CBF of 128 + 9% of control occurring at the 3 min measurement period. Thereafter, CBF declined in parallel with AMA. There

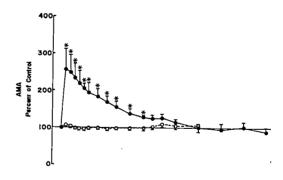
were also significant increases in PaCO2 following SCh (Fig 1); however, the PaCO2 increases could not account for peak CBF values (1).

Discussion. The present work demonstrates significant increases in CBF, AMA, and ${\rm PaCO}_2$ following SCh in dogs pretreated with "defasciculating" doses of pancuronium. agreement with humans studies (2), our data suggest that the presence or absence of fasciculations following i.v. SCh is not a reliable indicator of the cerebral response to SCh. Assuming our data in dogs are transferable to humans, these data suggest that pretreatment with defasciculating doses of pancuronium is not as effective as metocurine pretreatment (2) in preventing the cerebral response to i.v. SCh in lightly anesthetized patients.

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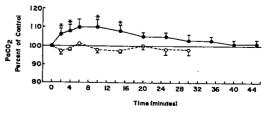


Fig. 1: CBF, AMA, and PaCO₂ following SCh versus placebo (Vertical bars represent one SE; N = 6 dogs.) Pre-SCh control values were CBF 94.6 \pm 14.7 ml·100g-1·min-1 and PaCO₂ 40 \pm 0 mmHg. Preplacebo control values were CBF 91.8 ± 12.3 ml·100g⁻¹·min⁻¹ and PaCO₂ 39 ± 0 mmHg. (* denotes p < 0.05 between SCh and placebo treatments).

THE EFFICACY OF DOXACURIUM CHLORIDE ECR ENDOTRACHEAL INTUBATION AND PROVISION OF NEUROMUSCULAR Title:

BLOCKADE IN PATIENTS ANESTHETIZED WITH ENFLURANE

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Introduction: Doxacurium Chloride (DOX) is a long-acting nondepolarizing N-M blocking agent with little or no cardiovascular side-effects currently undergoing clinical investigations in this country (1). Under balanced anesthesia ita ED95 is approximately 23 ug/kg. When administered as a bolus of 40 ug/kg, the time of maximum block occurs in 5 min with a clinically effectiv∋ duration of action of approximately 70 min (2). Therefore, this agent may be useful for N-4relaxation of intermediate and long duration. This study was designed to evaluate the intubating conditions provided by 2 different doses of DO (as a function of time. We also evaluated the onset, depth and duration of N-M blockade produce1 by DOX under enflurane, N20/02 narcotic anesthesia.

Methods: 35 patients were selected and enterel into this institutionally approved study after granting their informed consents. These patients were ASA class I or II who were to undergo elective surgical procedures of 2 or more hours in duration. The subjects ranged in age from 27 to 69 years old and weighed between 51 to 92 kg Patients were pre-medicated with 10 mg PO diazepam 45-60 min prior to induction. Anesthesia was induced with fentanyl (1-1.5 ug/kg) followed 2 mim later by thiopental (4-7 mg/kg). Maintenance of anesthesia was with N20/02 (70/30), enflurane (ET= 0.7), fentanyl and thiopental as needed Approximately 30 sec after induction, the isometric force of contraction of the adductor pollicis muscle was elicited utilizing & train-of-four (TOF) at 2HZ supramaximal impulses of 0.2 msec curation every 10 sec via surface electrodes placed over the ulnar nerve. The response of the adductor pollicis was quantitated with a Grass FT10 force transducer and continuously recorded on a Gould polygraph. After stabilization of the baseline twitch response (approximately 2 min after the induction dose of thiopental), a 0.05 mg/kg bolus of DOX was administered to Group I patients (n=9). Endotracheal intubation was attempted and conditions scored 4 min later. Patients in Group II (n=9) also received 0.05 mg/kg dose of DOX but intubation was attempted and scored 3 minutes later. Since the intubation condition in the majority of Group II patients were judged to b \in suboptimal, the Group III patients (n=9) wer€ given an 0.08 mg/kg bolus of DOX and intubation attempted and scored 3 min later. Group IV patients (n=8) received 0.08 mg/kg dose of DOX and intubation was attempted and scored 2.5 mir. later. All DOX injections were made over 5 sec. Additional doses of DOX were utilized when the first twitch of TOF (T_1) was recovered to 10-25% of its baseline value. Once N-M blockade was no longer required, reversal was attempted using either neostigmine 45 ug/kg, neostigmine 60 ug/kg or edrophonium 1000 ug/kg assigned on a random basis in combination with 1 mg atropine. One way ANOVA and Kruskal-Wallis test were used for statistical comparisons.

A p<0.05 was considered significant. Data is presented as mean (±SD).

Results: There was no significant difference in the demographic variables among the Groups. Table 1 summarizes the intubation data. Patients in Group I were easily intubated with intubating conditions rated good to excellent. The mean intubating score in Group I was 1.9 (0.33) which is based on a 1-4 scale where 1 is "excellent" and 4 is "rot possible". In Group II, intubating conditions were good in 2, poor in 6 and not possible in one patient. The difference in intubating conditions between Groups I & II were clinically and statistically significant. Patients in Group III were intubated with a mean score of 2.1 (0.8). The difference between Groups II & III was also clinically & statistically significant. Group IV patients had a mean score of 2.25 (0.89) which was not significantly different from those in Group III. There was no significant difference between Groups with the respect to the % T1 block prior to Intubation. The time from the administration of DOX to the onset of 90% of T1 block and maximum T_1 block was significantly shorter in patients receiving 0.08 mg/kg dose (n=17) than those receiving 0.05 mg/kg dose (n=18). In addition, the time from the administration of DOX to the start, 5% and 10% recovery of T_1 was also significantly prolonged in the patients receiving the higher dose. The Neuromuscluar Parameters are summarized in Table II.

Discussion: DOX is a potent nondepolarizing N-M blocking agent with a relatively long duration of action. It can be utilized to provide good-excellent intubating conditions 4 min after a single IV Bolus dose of 0.05 mg/kg. Higher doses (i.e. 0.08 mg/kg) are required if good intubating conditions are to be provided in less than 4 min. Recovery data obtained in this study is similar to those reported in an earlier study by Basta et al.

Table I - Intubation Data

Group	Intubation Score
I	1.9(0.3) a
II	2.9(0.6) a,b
III	2.1(0.8) b
IV	2.25(0.9)
a = p < 0.01	
b = p < 0.05	

Table II - Neuromuscluar Parameters

Time (min) to	0.05 mg/kg	0.08 mg/kg	P
90% block	5.4(1.6)	3.6(0.9)	<0.01
Maximum block	8.4(3.4)	5.7(1.3)	<0.02
start of recovery	34.3(16.5)	90(55.3)	
5% recovery	46.2(23.6)	99.1(31.4)	
10% recovery	55.7(24.3)	101.5(24.1)	<0.01

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- 3. Basta et al. Anesthesiology 65:A281, 1986

Title: PULSE OXIMETRY EVALUATION OF THE PALMAR CIRCULATION

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Introduction. Radial arterial cannulation, though a relatively safe procedure, can be associated with ischemic damage to the hand. In order to minimize this danger, various methods of substantiating the collateral circulation of the hand have been used. The usual method is by the Allen test. This test may be difficult to interpret because lack of patient cooperation, inadequate lighting, anemia, skin pigmentation and jaundice. In this study we evaluated the pulse detecting capability of the pulse oximeter in assessing the collateral circulation of the hand.

Methods. Thirty-one patients receiving radial artery cannulation for intraoperative monitoring were evaluated precannulation and postcannulation. The Allen's test was performed on the hand to be cannulated assessing both ulnar and radial collateral flow. Then pulse oximetry (501+, Criticare Systems, Inc.) evaluation of the circulation was performed. Placing the oximeter probe on the patients index finger, both radial and ulnar arteries were occluded until "no perfusion" registered on the oximeter. Compression over the radial artery was released and the time to pulse detection was noted. This procedure was repeated with release of pressure over the ulnar artery.

The Allen's test results were categorized as normal, indeterminate (no change in palmar coloration with occlusion of arterial perfusion), and abnormal when palmar flush took longer than 15 seconds to occur. Pulse oximetry results were categorized as abnormal if pulse detection did not appear within 15 seconds, from release of the measured artery. This was done just prior to cannulation with a 20 g, 2 inch nontapered catheter and three days post decannulation. Data were analyzed by Chi-square. Significance was considered present if p < 0.05.

Results. Thirty-one ASA II or III patients were studied of which 22 were male and 9 female. The mean age was 49.2 years (range 19-86). None had significant history of peripheral vascular disease.

Precannulation one patient had abnormal radial artery blood flow (RBF) and two had abnormal ulnar artery blood flow (UBF) by Allen's test as well as with the pulse oximeter. In 13 evaluations pulse oximetry showed normal radial and ulnar arterial blood flow while the Allen test was indeterminate, 6 for RBF and 7 for UBF.

Three days after the radial artery catheter was removed there were 8 abnormal Allen's test, 7 showing abnormal RBF and 1 abnormal UBF. Pulse oximetry confirmed the abnormal blood flow. There were 7 and 8 indeterminate Allen's test for UBF and RBF, respectively. Pulse oximetry showed normal perfusion in all of the indeterminate Allen's test after decannulation. Table 1 shows that pulse oximetry evaluation for collateral blood flow is significantly more sensitive than the Allen test.

Discussion. The pulse oximetry functions are dependent upon a pulsating arterial bed between light source and detector which in this case can be considered a multiple wave-length plethysmograph. Investigators have found this technique to correlate well with blood flow. We utilized this aspect of the pulse oximeter for conformation of adequate collateral circulation.

In this study, it was found that in those patients with either a clearly normal or abnormal Allen's test, there were no differences with the pulse oximeter evaluation. However, in the indeterminate cases the presence or absence of collateral circulation was easily established via the pulse oximeter.

The use of the commonly available pulse oximeters in assessing collateral circulation of the hand is a simple, easily applied method of improving the sensitivity of the Allen's test.

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Table 1. Comparison of Allen's Test to Pulse Oximetry in Detection of Collateral Circulation

	Precanni	ulation	Postcann	ulation
	Allens	P.O.*	Allens	P.O.*
Normal	46	59	39	54
Abnormal	3	3	8	8
Indeterminate	13	0	15	0

P.O. (pulse oximetry); *p < 0.001 when compared to the Allen's test Title:

EFFECTS OF ANEMIA ON PULSE OXIMETRY AND CONTINUOUS MIXED VENOUS OXYGEN SATURATION MONITORING

IN DOGS

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Introduction. Continuous arterial and mixed venous oxygen saturation are being utilized with increasing frequency in the intensive care unit and operating room. Both types of oximeters rely on an extension of the Beer-Lambert law using two c three wavelengths of light to determine the oxygen saturation of hemoglobin. These devices are used frequently in patients with acute hemorrhage \varpropto anemia during anesthesia but little data have yez been published on the possible effects of decreasing hemoglobin concentration on the accuracy $\sigma \overline{c}$ these monitors(1,2). On theoretical grounds one might expect decreasing accuracy with decreasing hematocrit. The purpose of this study is to assess the accuracy of pulse and reflectance oximetr during experimentally induced normovolemic anemia. Methods. Ten mongrel dogs (six female) weighing LD 20 kilograms were premedicated with 0.3 mg/kg acepromazine, anesthetized with intermittent pentabarbital, incubated and ventilated to normocarbia. A 16 gauge Jelco catheter and 8.5 Fr introduce were placed via a femoral cutdown into the femoral artery and vein respectively. A Shaw Opticata pulmonary artery catheter (PAC) (Oximetrix Corp. Mountain View, CA) was calibrated in vitro as per the manufacturer's instructions and then floated $\ \ \ \ \ \$ a wedge position by observing the pressure waveform. A Nellcor N-100 pulse oximeter (Nellcor. Hayward, CA) was applied to the dog's tongue with \pm Nellcor D25 Digit Oxisensor transducer. Pule oximeter data were collected when the pulse oximeter pulse rate equaled the EKG heart rate. Normothermia was maintained by use of a heating blanket, warmed I.V. fluids, and hot water bottles placed on the thorax and abdomen. Each data point included temperature, heart rate, blood pressure. pulmonary artery wedge and pressure, thermodiluti $\ensuremath{\square}$ cardiac output in triplicate, and arterial and mixed venous saturations. Oxygen saturations and analysis of blood samples on an IL 282 Co-Oximet∈ (Instrumentation Laboratories, Lexington, MA), acjusted for canine blood and calibrated daily using known standards. Hematocrit was determined for each point by spun capillary tubes.

At each level of hematocrit, measurements were mace at Fi02 values from 1.0 to 0.1. The hematocrit was then acutely lowered 5% by hemorrhaging the dog and replacing the lost volume with either 1:1 albumin or hetastarch or 3:1 crystalloid, adding enough to keep the pulmonary wedge pressure constant. This cycle was repeated until a hematocrit of 5% was reached or the dog expired.

Statistical analysis was performed as recommended by Bland and Altman and included calculations of bias and precision (3). Bias is the mean of the differences between the two measurements (e.g. IL 282 - Nellcor) and precision is the standard deviation of the differences.

Results. Table 1 summarizes the performance of the two monitors over the wide physiologic conditions

achieved in the dog model. Ninety-five percent confidence intervals (CI) for the bias are listed in the column labeled 95%.

Discussion. Inspection of the bias and the 95% confidence intervals for the Oximetrix PAC shows that the bias remains close to zero for hematocrits greater than 10%. Marked underestimation of the venous saturation occurs with hematocrits lower than 10%. The precision shows increased random error for hematocrits less than 25%, more so for hematocrits less than 15%. Similar degradation of performance of the pulse oximeter was seen for hematocrits less than 10%, with underestimation of the arterial saturation and greater scatter of readings. Otherwise, the pulse oximeter performed in a consistent fashion with a near zero bias. In severely anemic patients, (Hct < 15%) one should be aware that the estimates of either arterial or venous saturation by these monitors may be erroneous. However, for hematocrits down to 15%, both monitors provide consistent accuracy.

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Table 1. Bias and Precision of Oximetrix PAC $\,$ and Nellcor Pulse Oximeter.

Hct	Oximetrix PAC	N=193		
11	Bias ± SE	95% CI of Bias	Prec	#Pts
< 10	11.77 ± .98	9.6 to 13.9	3.4	12
10-14	-2.53 ± 2	-6.6 to 1.5	12	36
15-19	1.1 ± 1.3	-1.6 to 3.8	7.48	33
20-24	-1.02 ± 1.17	-3.3 to 1.3	7.3	39
25-29	-2.45 ± 1.1	-4.7 to2	5.49	25
30-34	$-2.93 \pm .75$	-4.5 to -1.4	3.89	27
35-39	-1.49 ± 1.03	-3.8 to 0.8	3.43	11
>40	-2.09 ± 1.8	-6.2 to 2	5.73	10
< 25	0.36 ± 92	-1.5 to 2.2	10.1	120
≥ 25	-2.43 ± 53	-3.5 to -1.4	4.6	73
	Į .			
Hct	Nellcor Pulse	Oximeter N=178		
11	Bias ± SE	95% CI of Bias	Prec	#Pts
< 10	5.40 ± 7.1	-12 to 22.8	18.8	7
10-14	-0.75 ± 0.7	-0.7 to 2.2	3.7	28
15-19	0.92 ± 1.04	-1.2 to 3.0	5.9	32
20-24	0.52 ± 1.1	-1.7 to 2.7	6.9	39
25-29	-0.25 ± 1.63	-3.6 to 3.1	7.8	23
30-34	-1.24 ± 1.29	-3.9 to 1.4	6.8	28
35-39	-5.46 ± 2.23	-10.4 to -0.5	7.4	11
≥ 40	0.37 ± 3.64	-7.9 to 8.6	11.5	10
< 25	-1.35 ± 0.94	-3.2 to 0.5	8	72
≥ 25	0.63 ± 0.71	-0.8 to 2.0	7.3	106
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Title : LEFT VENTRICULAR FUNCTION DURING PROPOFOL AND FENTANYL ANESTHESIA IN PATIENTS WITH CORONARY

ARTERY DISEASE. ASSESSMENT WITH A RADIONUCLIDE APPROACH.

Authors : JY Lepage, M.D., M Pinaud, M.D., C Juge, M.D., JH Hélias*, M.D., and A Cozian, M.D. Affiliation : Département d'Anesthésie-Réanimation Chirurgicale, and *Service de Médecine Nucléaire,

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Introduction. The combination of propofol (P) $\frac{1}{and}$ fentanyl (F) has been shown to block the sympathetic response to surgical stimulation in patients with coronary artery disease (CAD). But, the net result on hemodynamics of the cumulative negative chronotropic action of both P 2 and F 3 must be questionned. The present study investigated the effects of P as a sole anesthetic agent, and in combination with F on left ventricular (LV) function using gated radionuclide ventriculography (RNV) in unpremedicated patients with chronic CAD.

Methods. After approval by our local Ethics Committee and informed consent, ten ASA III patients (51-74 yr) undergoing major urologic surgery participated to this study. All patients suffered from documented angina pectoris secondary to CAD. None gave a history of congestive heart failure or valvular heart disease. No patients were premedicated, but all received their chronic medications (nifedining and isosophide) up to medications (nifedipine and isosorbide) up to and including the morning of surgery. The study was performed in the Nuclear Medicine Laboratory just before surgery. Heart rate (HR) was obtained from standard limb lead II of the ECG. A 7.5 Fr from standard limb lead II of the ECG. A 7.5 Fr thermodilution Swan Ganz catheter and a radial artery cannula were inserted under local anesthesia. All patients were studied by RNV using in vivo redd blood cells (RBC) labelling with 99m Technetium (Tc). A first RBC-Tc preparation containing 2-3 mCi of Tc was counted 10 cm apart from a gamma-camera. A first pass study was realized in the left anterior oblique position following the bolus iv injection of this source, allowing the evaluation of the isotopic dilution cardiac output (isot.CO) and the attenuation factor (AF). AF was assessed as the ratio: Q / (CxMTT) where Q = injected counts/s; C = integrated counts during the first transit; and MTT = factor (AF). AF was assessed as the ratio : Q / (CxMTT) where Q = injected counts/s ; C = integrated counts during the first transit ; and MTT = mean transit time of the bolus through LV during the first transit. Then, a second RBC-Tc preparation containing 20 - 25 mCi of Tc was iv injected. At equilibrium, 16 ECG-synchronized frames were acquired by a computer for processing. Mean end-diastolic (ED) counts, mean end-systolic (ES) counts, LVED and LVES areas, and ejection fraction (EF) were calculated each 1.5 min. Using the AF, ED volume (EDV), ES volume (ESV), stroke volume (SV), and densitometric CO (dens. CO) were obtained. The first dens.CO and isot.CO were compared for validation of the method in each patient. Three series of measurements including HR, mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), thermodilution cardiac output (th.CO), EF, EDV and ESV were collected, and derived values were calculated. A baseline study was performed before anesthetic induction (Awake). Aresthesia was induced with P (2 mg/kg) followed by an infusion of P (100 $_{\rm H}$ g/kg/min). Vecuronium (C.05 mg/kg) was administered, and ventilation (FIO2 : 1) was controlled (FECO2 : 4-4.5 %). After a period of 15 min, a second series of measurements was performed. The third series of measurements was undertaken 5 min after administration of F (5 $\mu g/kg)$. After the last data acquisition, the patient was transported in the operating room. All data are given as mean \pm SD. ANOVA and paired t test with Bonferroni correction were used for statistical analysis. The correlation between specific variables was tested with a linear regression method. P < 0.05 was considered as significant.

Results. The main results are summarized in the table. P alone produced significant decreases in MAP, PCWP, RAP, EDV, thermodilution cardiac index (th.CI) and thermodilution stroke index (th.SI). Following the addition of F, MAP, HR, th.CI and SVRI decreased significantly without changes in other parameters. There was a significant relationship between SI mesured by thermodilution tehcnique and densitometric measured SI $(y{=}0.47x{+}24.26\ ;\ r{=}0.60\ ;\ P{<}0.001)$.

	Awake	propofol	propofol + fentanyl
HR (b/∎in	71 <u>+</u> 14	68 <u>+</u> 11	57 + 8***
MAP (mmHg)	100 + 22	82 <u>+</u> 22**	53 <u>+</u> 9***
th.CI (1/min/m ²)	3.15 ± 0.68	2.43 ± 0.88**	1.88 ± 0.55**
th.SI (m1/b/m ²)	45.6 <u>+</u> 7.9	36 <u>+</u> 9**	34.2 <u>+</u> 7.6
SVRI (dyn.s/c $^{5}/^{2}$)	2495 <u>+</u> 432	2658 <u>+</u> 780	2215 <u>+</u> 491*
PCWP (makg)	6.1 <u>+</u> 2	3.1 <u>+</u> 3.2**	3.2 <u>+</u> 2.8
EDV (m1)	140 <u>+</u> 22	130 <u>+</u> 18*	127 <u>+</u> 16
ESV (ml)	61 <u>+</u> 13	56 <u>+</u> 15	56 + 11
EF (%)	55.4 <u>+</u> 5.8	57.6 ± 8.3	56.4 <u>+</u> 5.1

mean \pm SD; profopol vs awake *p<0.05;**p<0.002;***p<0.001;

propofol + fentanyl vs propofol *p< 0.005;**p< 0.002;***p< 0.001

Discussion. First-pass and equilibrium RN studies provided a complementary tool for assessment of cardiac performance during anesthesia. F in combination with P did not impair the LV performance in patients with chronic CAD not in cardiac failure. However, the decrease in HR may result in critical decreases in CI and in MAP. Consequently, caution should be exercised when F is administered during P anesthesia.

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- 3.Bovill JG et al : Anesthesiology 61:731-755,1984.

Title : LEFT VENTRICULAR FUNCTION DURING PROFCFOL ANESTHESIA IN PATIENTS WITH CORONARY ARTERY DISEASE :

ASSESSMENT WITH A RADIONUCLIDE APPROACH.

Authors : JY Lepage, M.D., M Pinaud, M.D., C JLce, M.D., JH Hélias*, M.D., and A Cozian, M.D. Affiliation : Département d'Anesthésie-Réanimation chirurgicale, and *Service de Médecine Nucléaire,

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Introduction. Radionuclide cineangiography effectively reproduces results obtained with contrast angiography in the assessment of left ventricular volumes and function and provides a complementary tool for assessment of cardiac performance during anesthesia. 2 This study was designed to evaluate the effects of the emulsion formulation of propofol (P) on left ventricular function (LV) using gated radionuclide ventriculography (RNV) and invasive cardiac monitoring in unpremedicated patients with chronic coronary artery disease (CAD).

Methods. After approval by our local Ethics Committee and informed consent, ten ASA III patients (51-74 yr), undergoing major urrologic surgery participated to this study. All patients suffered from documented angina pectoris secondary to CAD. None gave a hystory of congestive heart failure or valvular heart disease. No patients were premedicated but all received their chronic medications (nifedipine and isosorbide) up to and including the morning of surgery.
The study was performed in the Nuclear Medicine Laboratory just before surgery. Heart rate was obtained from standard limb lead II of the ECG. obtained from standard limb lead II of the ECG. A 7.5 Fr thermodilution Swan Ganz catheter and a radial artery cannula were inserted under local anesthesia. All patients were studied by RNV by means of the ECG gated, equilibrium blood-pool technique using in vivo red blood cell labelling with 99m Technetium (Tc). Lyophilized solution that contained 100 mg of stannous-pyrophosphate (TCK 7 CEA) was injected iv. A in vivo preparation containing 2 mCi of 99m Tc pertechnetate (Technetium CEA Elumat 300) was counted 10 cm apart from a gamma-camera. was counted 10 cm apart from a gamma-camera. A first-pass study was realised in the left anterior oblique position following the bolus iv injection of this source, allowing the evaluation of the isotopic dilution cardiac output (isot.CO) and the attenuation factor (AF). AF was assessed as the ratio Q/(C MITT) where $Q = \frac{1}{2} \frac{1}$ injected counts/s, C = integrated counts during the first transit and MTT = mean transit time of the bolus through left ventricule during the first transit. Then a second in vivo preparation containing 20 to 25 mCi was injected. At equilibrium, 16 ECG-synchronized frames were acquired by a computer for processing. Mean end-diastolic (ED) counts, end-systolic (ES) counts, LVED and LVES areas and ejection fraction (EF) were calculated each 1.5 minutes by the computer. By using the AF ED volumes (EDV), ES volume (ESV), stroke volume (SV) and densitometric cardiac output (deCO) were obtained. The first deCO and isot.CO were compared for validation of the method. Seven series of measurements including heart rate (HR), mean arterial injected counts/s, C = integrated counts during ments including heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), thermodilutior output (th.CO), EF, EDV and ESV were collected and derived values were calculated. A baseline study was performed before anesthetic

induction (Awake). Anesthesia was induced with P 2 mg/kg followed by an infusion of P 100 $\mu g/kg/$ min. Vecuronium (0.05 mg/kg) was administered and ventilation (FI02 : 1) was controlled (FEC02 : 4-4.5 %). The hemodynamic and densitometric measurements were performed between 1 and 2.5 min, 3 and 4.5 min, 6 and 7.5 min, 9 and 10.5 min, 12 and 13.5 min and 15 and 16.5 min. After the last data acquisition the patient was intubated and transported in the operating room. All data are given as mean + SD. ANOVA and paired t test with Bonferroni correction were used for statistical analysis. The correlation between specific variables was tested with a linear regression method. P < 0.05 was considered as significant.

Results. The main results are summarized in the table. There was a significant relationship between SI mesured by thermodilution technique and densitometric measured SI (y=0.61x+19.068; r=0.68; P<0.001).

		propo	fol
	Awake	3 min	15 min
HR (b/min)	71 + 14	73 + 12	68 + 11
MAP (mmHg)	100 + 22	87 + 22***	82 + 22**
th.CI (1/min/m2)	3.15 + 0.68	2.42 + 0.67***	*2.43 + 0.83*
th.SI (■1/ɔ/■2)	45.6 + 7.9	33.8 + 5.7***	36 + 9**
SVRI (dyn.s/cm5/m2)	2495 + 432	2829 + 749	2658 + 780
PCMP (mmHq)	6.1 + 2	2.6 + 2.2**	3.1 + 31.1**
EDV (=1)	140 + 22	129 + 18**	130 + 18*
ESV (=1)	61 + 13	56 + 15	56 + 15
EF (%)	55.4 + 5.8	56.9 + 7.3	57.6 + 8.3

mean + SD; vs awake *p< 0.05; **p< 0.002; ***p< 0.001

Discussion. In CAD patients with good EF and PCWP < 12 mmHg, anesthesia with propofol was accompanied by a reduction in arterial pressure, exclusively due to a decrease in CI because of a decrease in SI related to a decrease in preload (PCWP and EDV). These findings are in accord with Stephan published data. 4 The fact that HR did not change in spite of the decrease in MAP had been reported 3 but the influence of P on HR is unclear and controversial: central vagotonic action cr change in baroreceptor reflex function. Contrary to the study of Caotes, 1 P did not influence SVRI which is an unreliable index of LV afterload. Absence of increase in EDV and ESV and absence of decrease in EF argue against the P-induced depression of cardiovascular function.

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Title:

PHARMACOKINETICS OF INTRAVENOUS DANTROLENE IN MALIGNANT HYPERTHERMIA SUSCEPTIBLE (MHS)

PEDIATRIC PATIENTS

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Introduction: Prophylactic intravenous dantrolene (2.4 mg/kg) has been recommended for MHS patients undergoing surgery. Although the pharmacokinetics of intravenous dantrolene in adults have been investigated, similar data in pediatric patients remain undetermined. Therefore, we investigated the pharmacokinetics of intravenous dantrolene in a cohort of MHS children.

Methods: With approval from the Human Review Committee, informed written consent was obtained from the parents of seven MHS pediatric patients scheduled for elective dental or ear-nose-throat surgery. MH susceptibility was based upon a previous history of masseter spasm or an MH reaction in the patient or a family history of a positive muscle biopsy or MH reaction. Each patient was ASA II, fasting and unpremedicated.

General anesthesia was induced with intravenous thicpental, atropine, atracurium and fentanyl and was maintained with 70% nitrous oxide in oxygen and intravenous diazepam. Each patient was monitored with a precordial stethoscope, blood pressure cuff and radial artery doppler probe, electrocardiogram, end-tidal pCO2 analyzer, rectal and axillary temperature probes and a pulse oximeter. End-tidal pCO2 was maintained at 30-35 mmHg. Free-flowing venous blood gases were analyzed during the study period.

After 10-15 minutes of anesthesia, 2.4 mg/kg intravenous dantrolene was infused over 10-12 minutes. At the completion of the infusion, eleven venous blood samples (3 ml) were collected at 1, 5, 10, 20, 30, 60, 120, 240, 480, 720, and between 1000 and 1500 minutes after the infusion from a large antecubital intravenous cannula. Each 3 ml sample was stored at $-20^{\circ}\mathrm{C}$ in a heparinized vacutainer tube until analysis.

After surgery, each patient was monitored with an electrocardiogram and apnea monitor in the recovery room overnight.

Grip strength was tested pre- and post-operatively by squeezing a 3 inch rolled blood pressure cuff which had been inflated to 40 mmHg.

The blood concentration ($\mu g/ml$) of dantrolene was determined using HPLC. The shape of the concentration-time profiles made it inappropriate to fit them to a compartmental model (see results). Therefore pharmacokinetic variables were calculated according to standard noncompartmental methods.

Results: The mean (+ SD) age and weight for the seven patients was $3.\overline{24}$ (+ 0.56) years and 15.9 (+ 1.4) kg respectively. Peak blood concentrations (nean + SD) 5.74 + 0.66 µg/ml occurred at 1 minute after the end of the dantrolene infusion. During the next 60 minutes, blood concentrations declined rapidly to reach a mean (+ SD) of 3.51

($\frac{+}{2}$ 0.36) μg/ml. During the 60-240 minute period after the infusion, the blood concentrations either remained constant or increased slightly in 5 of the 7 patients. After 240 minutes, the concentrations decreased following first order kinetics ($r^2 > 0.980$). The mean ($\frac{+}{2}$ SD) half-life determined from 240 minutes onwards was 9.8 ($\frac{+}{2}$.9) hours (range 6.3-14.8). The total body clearance (mean $\frac{+}{2}$ SD) of dantrolene as related to body weight was 0.700 ($\frac{+}{2}$ 0.167) ml/min/kg. The volume of distribution (Vdss) (mean $\frac{+}{2}$ SD) was 0.588 ($\frac{+}{2}$ 0.036) L/kg. The time interval until the blood concentration of dantrolene decreased to 3.0 μg/ml was (mean $\frac{+}{2}$ SD) 5.23 $\frac{+}{2}$.19 hours.

There were no abnormal blood gases, temperatures, MH reactions, arrhythmias or apneas, during the anesthetic or post-operative period in any patient. Only two patients cooperated in performing grip strength measurements post-operatively.

Discussion: The present study of dantrolene in pediatric patients differs from the previous study in adults2 in that in the present study dantrolene (2.4 mg/kg) was given as a rapid infusion whereas in the previous study it was administered intravenously in incremental doses over a 2-3 hour period. This difference in drug administration accounts for the increase in the maximum blood concentration observed in the present study. This difference may also account for the decrease in the time to reach 3.0 μ g/ml (the proposed minimum effective blood concentration) and the shorter terminal elimination half-life in pediatric patients but requires further studies to determine its significance. However, the two studies were similar in that the blood concentration of dantrolene was maintained at approximately 3.6 µg/ml from approximately 1-4 hours after completion of the infusion.

We conclude that a rapid intravenous infusion of dantrolene (2.4 $\mu g/kg)$ produces safe and predictable blood concentrations for MH prophylaxis in pediatric patients. However, the increased clearance of dantrolene indicates that supplemental doses of intravenous dantrolene may be required at more frequent intervals in pediatric patients than in adults.

 $\begin{tabular}{ll} \underline{Acknowledgement:} & We thank Norwich-Eaton \\ Pharmaceutical Inc. for performing the dantrolene \\ analyses. \\ \end{tabular}$

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TITLE

VECURONIUM FOR OUTPATIENT SURGERY

AUTHORS:

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INTRODUCTION. Ambulatory surgery is usually of short duration which may require profound muscle relaxation for as short a period as 10-30 min. Vecuranium (Norcuron) should be appropriate in outpatient surgery as it has a short duration of action and is shown to be devoid of serious cardiovascular side effects. 1,2 The present study was designed comparing vecuronium in outpatient surgery in 2 different anes-

thetic techniques.

METHOD. Forty (40) male and female adults, 18-75 years of age, ASA status I & II scheduled for a variety of elective outpatient surgical procedures were included in this study after signing informed consents. The study was approved by the committee on numan research. Patients received vecuronium (0.05 ng/kg) for tracheal intubation and abdominal relaxation and were randomly assigned into 2 grous: 1) ϵ palanced anesthetic group, 2) an inhalational anesthetic group. All patients received 4 mg/kg thiopental for induction and no premedication was given to any patient. Maintenance in the balanced group was with nitrous oxide 66% in oxygen supplemented by fentany I is needed to provide adequate anesthesia. lation anesthetic group was treated exactly the same is the other group, except the anesthesia was maintained with Isoflurane, in 2L N2O + 2L O2 (no fentany I) between 1 and 2% inspired. In both groups, pyridostigmine 100 mcg/kg and atropine 8 mcg/kg was used for reversal of neuromuscular blockade. In this clinical setting, a peripheral nerve stimulator was used to monitor each patient's degree of neuromuscular olockade using train-of-four (with 2Hz and 30mA) technique. Particular neuromuscular parameters noted vere: a) Onset time (time between start of injection of intubating dose and dimunition of T4); b) Time to 30% depression of twitch (when only T1 remains); c Max. twitch depression (when no twitch response occurs or when T1 was most depressed); d) Clinical duration (time from max. twitch depression to return of T1): 2) Recovery rate (time for recovery from T1 to T3);
f) Duration of neuromuscular block (start of intubating dose the time when T4 was noted). Conditions for intubation on a scale of 0-3 and duration of anestresia were also noted. (3 = Excellent - Jaw relaxed, /ocal cords apart and immobile, no diaphragmatic mcvenent - "bucking"; 2 = Good - Condition as in #3, e>-cept that there is some diaphragmatic movement -'bucking"; 1 = Jaw relaxed, cords moving, "bucking';) = Inadequate - Jaw not well relaxed, cords closec.)

RESULTS. Table I contains the demographic data. Table II contains the total thiopental and fentany T loses used in each group. Table III contains the cata obtained from the two groups. It appears the onset time for the vecuronium-isoflurane group is increased over the fentanyl group (173 sec \pm 40 to 148 sec \pm 39 respectively, P = < .05). There were no statistical differences between the two groups in respect to 90% depression, maximal twitch depression and recovery rate. Total duration of block was approximately the same for both groups (22.5 min \pm 4.6 fentanyl vs 22.4 $nin \pm 4.7$ Isoflurane).

DISCUSSION AND CONCLUSION: Our data suggests that the use of a small dose of vecuronium (0.05 mg/kg) is quite suitable for patients undergoing a variety of outpatient surgical procedures lasting not more than 10-30 min. regardless if one uses a narcotic (fentanyl) or inhalation (Isoflurane) technique which in theory is supposed to increase the action of relaxants. view of the fact that vecuronium's duration of block at this dose lasts approximately 22 min., it would seem that in this setting, low dose vecuronium is very appropriate for short outpatient procedures. Outpatient surgical procedures are those which require a short period of profound relaxation. Longer acting non-depolarizing muscle relaxants will probably outlast these short procedures. Newer shorter acting non-depolarizing relaxants such as vecuronium may serve a better purpose for these surgeries, offering stable cardiovascular parameters and causing no muscular pain after administration such as that which occurs with succiny?choline, a commonly used agent in short procedures.

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IARLE I	DEMOGRAPH	<u>IC DATA (mean ±</u>	<u>(S.D.)</u>	
Class ASA 15-1/5-II	Age (yrs) 36.4 ± 13.3	<u>Wt. (kg)</u> 71.8 ± 16.9	Ht. (in)	Operative Time (min) 46.8 ± 17.0
Vec. (Fent.) 18-1/2-II Vec. (Iso.)	37.9 ± 12.2	67.7 ± 13.2	63.4 ± 2.7	55.6 ± 16.1

The ages, heights and weights of the 2 groups are similar. Operative times for the Isoflurane group are increased over the fentanyl group, but not significantly.

TABLE II			
	Relaxant Dose (mg/kg)	Thiopental Dose Total (mg/kg)	Fentanyl Dose (mcg/kg)
Vec. (fent.)	0.05	6.4 ± 2.1	5.2 ± 1.8
Vec. (Iso.)	0.05	4.7 ± 0.9	_

Thiopental and fentanyl doses are the mean \pm S.D.

		Fentany l		Isoflurane		
	$\overline{\mathbf{x}}$	<u>+</u> S.D.	S.E.	x	<u>+</u> S.D.	S.E.
Onset time (sec)	148	± 39	9	173	± 40	9
90% depression (sec)	368	<u>+</u> 106	24	339	<u>+</u> 111	25
Max twitch depression (sec)	432	<u>+</u> 105	24	395	<u>+</u> 117	26
Clinical duration (min)	17.2	<u>+</u> 3.3	0.7	16.3	<u>+</u> 4.8	1.1
Recovery rate (min)	6.5	<u>+</u> 6.2	1.4	7.9	<u>+</u> 7.1	1.6
Total duration of block (min)	22.5	+ 4.6	1.0	22.4	<u>+</u> 4.7	1.1

Title: CONTROL OF CHRONIC SPASTICITY FOLLOWING SPINAL CORD INJURY USING INTRATHECAL MORPHINE

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INTRODUCTION: The use of intrathecal morphine (M) in the management of acute and chronic pain is well established (1). Struppler et al (2) showed that epidural M reduced muscle tone and abolished reflex spasms associated with multiple sclerosis. More recently, Erickson et al (3) demonstrated the effects of intrathecal M on spasticity associated with multiple sclerosis and spinal cord pathology. This study was performed to evaluate the effects of intrathecal M on chronic spasticity in patients with spinal cord injury (SCI).

 $\begin{array}{lll} \underline{\text{METHODS}}\colon & \text{Approval by the Institutional Human} \\ \text{Research} & \text{Committee} & \text{and} & \text{informed consent were} \\ \text{obtained.} & \text{Seven patients (M=5, F=2), with stable,} \end{array}$ non-progressive incomplete SCI of greater than 18 months duration were studied. Each patient had severe tonic and phasic spasticity of the lower extremities and trunk musculature with or without pain that significantly interfered with daily living and was not amenable to control using standard treatment methods. In Stage 1, a bolus dose of 1.0 mg of preservative-free M was injected intrathecally via the L4-5 interspace. Pain and spasticity were evaluated using spasticity grading and a visual analog scale, prior to and at frequent intervals after the injection. In Stage 2, a 24g catheter was inserted via a lumbar 20g Tuohy needle into the subarachnoid space and connected to an external pump. A continuous intrathecal infusion of M was commenced at an initial rate of 0.5 mg/day. Spasticity was evaluated daily using spasticity grading, polyelectromyography (poly-EMG) and isokinetic dynamometry (Cybex). The rate of infusion was adjusted in 0.5 mg/day increments until optimum spasticity control was obtained. In Stage 3, a subcutaneous infusion reservoir (pump) connected to an intrathecal catheter was surgically implanted and percutaneously filled with Mafter recovery from surgery and anesthesia. Following hospital discharge, patients were seen monthly on an outpatient basis for 12 months which included refilling the reservoir with M and spasticity assessments. In 2 additional SCI patients (M=2), undergoing reconstructive plastic surgery for decubitus ulcers, intrathecal M was temporarily administered as described for Stage 2 in order to decrease severe postoperative phasic spasticity.

RESULTS: In Stage 1, 6 patients demonstrated significant reduction in tonic and phasic spasticity. The earliest effects were noted 3-4 hours following M injection, reaching a maximum at 6 hours, gradually declining over the next 4-6 hours, with "carry-over" effects present 24 hours following injection. No change in spasticity was observed in one patient. Pain associated with spasticity was decreased in 6 patients, but

aggravated in one patient with lower extremity burning dysesthesia. Side-effects, i.e., itching, nausea, and vomiting were present in 5 patients. Three patients elected to continue with Stage 2. In 2 patients, optimum control of phasic and tonic spasticity was achieved with 1 mg/day, while one patient required 3 mg/day. Phasic and tonic spasticity as judged by clinical measures, poly-EMG and Cybex were optimally controlled at these dosages with the incidence of side-effects being significantly less. Two patients elected to proceed with Stage 3. One patient obtained significant reduction in spasticity for the 12 month period, although requiring an increase in M dosage from 1 mg/day to 3 mg/day after 8 months. The other patient developed gram-negative septisemia secondary to a urinary tract infection with death 2 days following hospital discharge. Two additional postoperative patients required 1 mg/day for 5 and 8 days respectively, demonstrating reduction in spasticity, and beneficial effects on the surgical wound. In all patients receiving a continuous infusion of M (n=5), a clear dose-response pattern was not observed.

DISCUSSION: These results demonstrate that intrathecal M reduces spasticity associated with SCI in agreement with others (3). The intrathecal route, while providing adequate spasticity control permits the use of small amounts of drug, thus minimizing the incidence of side-effects. The continuous administration of intrathecal M over a prolonged period of several months using implantable infusion pumps has not been associated with tolerance phenomena (3). The exact mechanism for the effects of intrathecal M on spasticity is, however, not clear. Spinal opioid receptors are associated with a variety of systems in addition to those pertaining to sensory modulation. Electrophysiologic studies have shown the opiates inhibit polysynaptic reflexes and to a lesser degree monosynaptic reflexes and alpha-motoneuron firing (4).

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Title: EFFECTS OF DIAGNOSTIC SPINAL ANESTERSIA IN CHRONIC PAIN FOLLOWING SPINAL CORD INJURY

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INTRODUCTION: Chronic pain following spinacord injury (SCI) is a complex diagnostic problem often regarded as "phantom" or "psychogenic" in nature (1). However, the response to spina anesthesia may clarify whether the pain is "real or "neurogenic." This study was performed to evaluate the effects of spinal anesthesia of chronic pain following SCI and determine whether it was an effective diagnostic modality.

METHODS: Eleven SCI patients with chroni-pain were referred for diagnostic spina Approval from the Institutiona anesthesia. Research Committee and informed consent wer-obtained. An intravenous line was started anvital signs monitored continuously. Patients werplaced in the right lateral position and the areover the lumbar vertebral spine prepared wit betadine for 15 minutes. Using strict asepsis, -23g polyethylene catheter was inserted 3 cm intrathecally via a 20g Tuohy needle placed in the L4-1 lumbar interspace and taped in position. With the patient supine, a baseline pain assessment wa: performed, i.e., visual analog scale (VAS), pair distribution (diagrammatic), quality and intensity of pain, sensory level (pin-prick), altered sensations. In each patient, three separate injection: of 3 ml preservative-free normal saline (placebe (P)) 5% lidocaine (L) in dextrose (hyperbaric) and 0.4% tetraceine (T) in dextrose (hyperbaric) double blind and in random sequence, were performed via the catheter. Local anesthetic (LA. was administered in aliquots every 5 minutes in ar attempt to obtain a sensory level above the patient's SCI. The maximum doses of L and T were 100 mg and 20 mg, respectively. Following the administration of P and LA, pain assessments were performed every 15-30 minutes. In 5 selected patients, neurophysiologic monitoring (NMON) of residual motor function was performed in conjunction with the pain assessments, i.e., H and bulbocavernosus reflexes, patellar tendon and ankle jerks. Assessments continued until the patient's symptomatology and neurophysiologic parameters of motor function returned to pre-spinal anesthetic status. The results were statistically analyzed for significance using the Student's t test.

RESULTS: The results are shown in Table 1. Two patients withdrew from the study following E and L administration, due to temporary worsening of pain after intrathecal lidocaine, and the development of an urinary tract infection. Adverse hemodynamic responses or complications did not occur in any patients. Three patients demonstrated placebo responses to intrathecal saline. These included a significant decrease in pain and change in altered sensation. However, 8 patients reported no change in pain or altered sensation in response to P. Following L administration, E patients reported a decrease in pain while I patients reported no change. In contrast, only I patients demonstrated a decrease in pain following T administration, with 6 patients reporting no

change. The duration of reduction in pain was 200.7 ± 36.8 and 220 ± 22.1 mins (difference of 19.3, p = NS) for L and T, respectively. A sensory level of anesthesia above the level associated with SCI was observed in 2 patients. NMON demonstrated that spinal reflexes remained unchanged following saline, but were inhibited in all 5 patients following LA administration.

DISCUSSION: The results of this study have verified the complex nature of spinal cord injury pain. Consistent responses to either L, T or P were not observed. Prolonged duration of LA action, demonstrated by both pain assessments and clinical neurophysiologic monitoring, suggests increased sensitivity or prolonged clearance of LA from the intrathecal space. The inability to obtain a sensory level of anesthesia above the SCI level in the najority of patients indicates obstruction within the spinal canal. The results of this study differ from a previous report (2), in which a sensory level of anesthesia was obtained above the SCI level. Although each patient's response to spinal anesthesia must be individually assessed, objective conclusions about whether pain is "psychogenic" or "neurogenic" in origin should be carefully evaluated. Spinal anesthesia may not be a useful diagnostic modality for chronic pain in this patient population. The reasons for this are unclear but may be related to anatomic and biochemical changes in the intrathecal space below the level of injury, neurophysiologic mechanisms responsible for the pain or type of LA.

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Table 1. CHRONIC SCI PAIN: RESPONSE TO SPINAL L, T, and P WITH NMON.

Pt.	L		Т		P	NM	0N * *
	%d	D	%d	D		LA	D
1	100	180	NC		-		
2	NC		NC		-		
3	NÇ		25	120	-		
4	75	250	NC		+	T	135
5	60	150	NC		+	T	120
6	50	90	*		-	L	100
7	25	150	75	180	+	L	120
8	75	360	80	360	-		
9	75	105	*		-		
10	75	270	NC		-		
11_	NC		NC			L	180
Mea	n 66.8	200.7	43.3	220			
SEM	7.8	36.8	18.3	22.1			
~ .	· o .	• •	2	17	- D.	+:	(-i-)

%d = % decrease in pain

D = Duration (min)

* = Pt. withdrew from study NC = No change

** = D of reflex inhibition

Title: DOES pH ADJUSTMENT REVERSE NESACAINE ANTAGONISM OF POSTCESAREAN EPIDURAL FENTANYL ANALGESIA?

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Introduction. The choice of local anesthetic has been reported to affect postcesarean epidural fentanyl analgesia. The mechanism of this antagonism has not been determined. This study was designed to identify what effects, if any, the alkalinization of the commercial preparation of 2-chloroprocaine has on later epidural fentanyl analgesia.

Methods. Twenty-one ASA Class I or II parturients for repeat cesarean delivery requesting epidural anesthesia (after consenting to an institutionally approved protocol) were randomly assigned to receive either 3% Nesacaine (N), or alkalinized 3% Nesacaine (CN). Surgical epidural anesthesia was induced to T2-T4 sensory level and maintained as dictated by standard clinical practice. At the end of surgery the sensory level of anesthesia and a linear visual analog pain score were obtained immediately before the injection of 50 ug of fentanyl, and every 30 minutes thereafter by a blinded observer. Data was subjected to Analysis of Variance using a Duncan Waller test.

Results. Analgesia was characterized by the time to the first request for narcotic (TFN) and the duration of a 0 pain score (DURO). These time intervals were measured from the injection of the epidural fentanyl. The time to regression of the sensory anesthesia to below L1 was measured (TL1). This time interval was measured from the last "top up" injection of local anesthetic during the surgical anesthetic.Duration of narcotic analgesia independent of local anesthetic sensory anesthesia (An-S) was defined as the time interval from regression of anesthesia to the first request for narcotics. If a patient requested narcotic analgesia before the sensory block regressed to below T-12, an An-S score of zero was assigned.

Fentanyl did not produce analgesia (An-S) independent of the sensory local anesthetic block of N. There was no statistical difference from N in DURO, TFN, TL1 or An-S when CN was used. At a significance

level of .05, this sample size was sufficient to give an 80% probability of detecting a difference in DURO, TFN, TL, or An-S.

DRUG	N	CN
(mean <u>+</u> SD)		
DURO (min)	56±15	52±19
TFN (min)	85±27	73±26
TL1 (min)	103±27	117±57
An-S (min)	1.5±5	1±2

There was no difference in the height, weight, age, gestational age or the 24 hour narcotic requirements in each of the patient groups.

<u>Discussion.</u> The choice of local anesthetic does influence the efficacy of postcesarean delivery epidural fentanyl analgesia. It was observed that the duration of opioid analgesia independent of local anesthetic sensory anesthesia was far less than one hour in all patients receiving 3% Nesacaine or alkalinized 3% Nesacaine. In our patient population there seems to be no clinically significant period of opiate analgesia (An-S \leq 1 hour). Though N has long been known to affect the subsequent anesthesia with amide local anesthetics, it has only recently been reported to affect opiate induced analgesia in the neuraxis. The mechanism for this apparent antagonism has been postulated to be a change in the pH induced by the N (pH 3.3-5.3) or its metabolites. We have not been able to overcome this antagonism with pH adjustment suggesting that the pH change is not the basis for the observed antagonism.

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- Corke B, Carlson CG, Detbarn WD. The influence of 2-chloroprocaine on the subsequent analgesic potency of bupivacaine. Anesthesiology 1984; 60:25-30.

Title:

ANESTHETIC CHOICE AFFECTS POSTCESAREAL EPIDURAL FENTAMYL ANALGESIA

Authors:

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Introduction. This study was designed to confirm the efficacy of epidural fentanyl analgesia after variou epidural local anesthetic preparations in clinical use today.

Methods. Thirty ASA Class I or II parturients for repeat cesarean delivery requesting epidural anesthesia (after consenting to an institutionally approved protocol were randomly assigned to receive either (1) 0.5% bupivacaine (B), (2) 2% lidocaine with epinephrine 1:200,000 (L/E), or (3) 3% Nesacaine (N). Surgica epidural anesthesia was induced to T2-T4 sensory leve and maintained as dictated by standard clinica practice. At the end of surgery the sensory level or anesthesia and a linear visual analog pain score were obtained immediately before the injection of 50 ug or fentanyl, and every 30 minutes thereafter by a blindec observer. Data was subjected to Analysis of Variance using a Duncan Waller test.

Results. Analgesia was characterized by the time to the first request for narcotic (TFN) and the duration of a 0 pain score (DURO). These time intervals wer∈ measured from the injection of the epidural fentanyl. The time to regression of the sensory anesthesia to below L1 was measured (TL1). This time interval was measurec from the last "top up" injection of local anesthetic during the surgical anesthetic. Duration of narcotic analgesia independent of local anesthetic sensory anesthesia (An-S) was defined as the time interval from regression of anesthesia to the first request for narcotic.

Fentanyl did not produce analgesia (An-S) independent of the sensory local anesthetic block of N.

DRUG (mean + SD)	В	L/E	N
DURO (min)	133+71	100+48	56+15 *
TFN (min)	233±47	192±54	85±27*
TL1 (min)	261±52	188±29	103±27*
An-S (min)	35±44	54±56	1.5±5*
*statistically sig	gnificant diffe	erence $(p < 0.$.05)
from LE or B		•	

There was analgesia that outlasted the sensory local anesthetic block for patients receiving L/E and the patient receiving B. The duration of the analgesia (An-S) for the patients receiving B and L/E was one hour or less. There was no difference in the height, weight, age, gestational age or the 24 hour narcotic requirements in each of the patient groups.

The choice of local anesthetic does Discussion. influence the efficacy of postcesarean delivery epidural fentanyl analgesia. Though N has long been known to affect the subsequent anesthesia with amide local anesthetics, 3 it has only recently been reported to affect opiate induced analgesia in the neuraxis.² The mechanism for this apparent antagonism has been postulated to be a change in the pH induced by the N (pH 3.3-5.3) or its metabolites. The time to the regression of the sensory anesthetic block to below the T12 dermatome was significantly longer in patients receiving B or L/E from those receiving N. There may be a prolongation of the local anesthetic sensory block by the opiates. Such synergism has not been investigated here. It was observed that the duration of opioid analgesia independent of local anesthetic sensory anesthesia was less then one hour in all patients. In our patient population there seems to be no clinically significant period of opiate analgesia (An-S < 1 hour).

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Title:

MONITORING OF SOMATOSENSORY EVOKED POTENTIALS DURING TEMPORARY ARTERIAL OCCLUSION IN

CEREBRAL ANEURYSM SURGERY

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Introduction. Somatosensory evoked potentials (SSEP) have been used during cerebral aneurysm surgery to monitor brain function ^{1,2}. The purpose of our present study was to evaluate the effectiveness of SSEP monitoring as a predictor of the neurological outcome during temporary arterial occlusion in patients undergoing cerebral aneurysm surgery.

Methods. After institutional approval, 62 patients undergoing cerebral aneurysm surgery were monitored intra-operatively with SSEP. Anesthesia was induced with thiopentone, fentanyl, lidocaine and succinylcholine. Maintenance of anesthesia consisted of 50% nitrous oxide/50% oxygen or air/oxygen and isoflurane. Induced hypotension was frequently used during dissection of the aneurysm, but whenever temporary occlusion of an artery was performed, blood pressure was returned to normal. SSEP were recorded from the somatosensory cortex (C3' and C4') as well as from C7 spine or Erbs point in response to median nerve stimulation with a square wave at 15 mamp. Bilateral control SSEP were recorded after induction of anesthesia and during stable anesthesia. Throughout the periods of dissection, temporary occlusion of the feeding artery and clipping of the aneurysm SSEP were continuously monitored up to the end of the surgical procedure. The SSEP recordings were analyzed using both the amplitude of the cortical peak (N20) and the central conduction time (CCT) (N20-N13). Changes in SSEP were correlated to postoperative neurological deficits.

Results. SSEP recordings were obtained in 62 patients with 67 aneurysms (22 males and 40 females). The mean age was 48 years with a range of 26-71 years. Temporary occlusion of the feeding artery was used in 40 patients. The significant findings of the patients with temporary occlusion are shown in the Table. The SSEP changes considered clinically significant were a decrease in amplitude > 50% of N20 and/or an increase in CCT > 1 msec. These changes also had to be unilateral and ipsilateral to the side of temporary occlusion. Bilateral changes were considered to be due to effects of anesthetic drugs or physiological factors such as temperature change. In Group I, one patient had no change on SSEP monitoring, but developed a neurodeficit in the Recovery Room. CT Scan showed a large epidural hematoma and after evacuation of the hematoma, the deficit resolved. In Groups 2 and 3, two patients had persistent SSEP changes and they both developed neurodeficits. Eleven patients had reversible SSEP changes, and only three of these had transient neurodeficits postoperatively. The time of onset of the

maximum SSEP change after temporary occlusion occurred from 2.5 to 10 minutes and recovered after the release of the occlusion in all except the two patients with persistent changes. The duration of the occlusion ranged from .5 to 15 minutes, and in most patients there were multiple occlusions of short duration. Three patients in whom no temporary occlusion was used had reversible SSEP changes which occurred during brain retraction and induced hypotension; one patient developed a postoperative deficit.

Discussion. We have demonstrated that SSEP monitoring is feasible during cerebral aneurysm surgery and useful when temporary occlusion of a major artery is required. The occurrence of a persistent change in SSEP, either a decrease in amplitude of N20 > 50% or an increase in CCT > 1 msec correlates well with neurodeficits postoperatively. In the patients who had reversible SSEP changes, only 27% developed a neurodeficit. Thus, a reversible change cannot be used to definitively predict the development of a deficit. This can be explained partly by the fact that the temporary occlusion of the artery was of short duration in most of the cases and the SSEP change recovered promptly after the release. The duration of a SSEP change that predicts cerebral injury is unknown. The clinical outcome is expected to be good if the change in SSEP recovers in a short time after occlusion. In conclusion, intra-operative monitoring of SSEP is useful in the assessment of the neurological integrity of specific neural pathways during the temporary occlusion of an artery.

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TABLE				
GROUP	SSEP CHANGE	REVERSIBLE CHANGE	PERSISTENT CHANGE	NEURO DEFECIT
1	No Change (n = 27)	0	0	1
2	↓amplitude > 50% (n = 6)	5	1	2
3	1CCT > 1.0 msec (n = 5)	4	1	3
4	lamplitude and fCCT (n = 2)	2	0	0
TOTAL	(40)	11	2	6

Title: HEMOSTASIS MARKERS IN CARDIAC SURGER PATIENTS FOLLOWING POSTOPERATIVE AUTOTRANSFUSION

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Introduction. Mediastinal shed blood (MSB) is used for postoperative autotransfusion to decrease requirements for banked blood transfusion and its associated risks ¹. To assess the value of this practice at our institution we measured hematocrit and platelet counts in MSB and in patients' plasma before and after autotransfusion. In an attempt to determine if autotransfusion might contribute to coagulation abnormalities in cardiac surgery patients we characterized MSB using new specific hemostasis markers. These parameters were measured in patients' plasma before and after autotransfusion to determine if clotting was affected.

Methods. The use of human subjects was approved by the hospital medical research committee and informed consent was obtained from all patients. Ter patients who underwent cardiac surgery on extracorporeal bypass under high dose narcotic anesthes vere studied. Mediastinal shed blood was collected using the Sorenson Receptal ATS System (Sorenson Research Corporation, Salt Lake City, Utah). In the immediate postoperative period MSB was the only rec cell product given. Patient samples were drawn by renipuncture postoperatively before and fifteen minutes after autotransfusion. Samples of the MSB were taken after 40 micron filtration from the end of standard blood infusion tubing. Samples were malyzed for hematocrit and platelet counts using in automated cell counter. Plasma levels of Platel=: factor 4 (Pf 4), Beta-thromboglobulin (BTG), and ibrinopeptide A (FPA) were determined using tandard radioimmunoassay techniques. Fibrinogen plit products (FSP), D-dimer (Dd) and antithrombin II (AT III) were measured using an automated entrifugal analyzer (Instrumentation Laboratories, exington, MA). Data was analyzed using a paired

Results. Immediate postoperative autotransusion volumes ranged from 200 to 500 ml. (mean 313 l.). MSB had a mean hematocrit of 16.6 ± 3.9% and mean platelet count less than 20,000. There was o statistically significant change in either of hese parameters between the pre— and post—auto-ransfusion patient sample times. MSB contained ery high levels of Pf 4, BTG and FPA. There was o significant change in patients' plasma levels of hese markers after autotransfusion. FSP were levated in the MSB (256 ng/ml) and increased from 27.2 ± 7.7 to 147.2 ± 60.7 ng/ml) in patients ollowing autotransfusion (r .05). D—dimer was lso elevated in MSB and showed a similar increase ollowing transfusion. AT III levels were low in

the MSB and there was no change in patients' plasma levels of this protein following autotransfusion.

Discussion. Reports published during the late 1970s suggested MSE for autotransfusion had hematological characteristics similar to whole blood 2. Our results concur with other investigators suggestion MSB is very dilute and does not significantly increase patients hematocrits or platelet counts³. Therefore use of MSB as a primary source of blood cell replacement may not be beneficial. It has been suggested that MSB may be "partially clotted" and massive transfusion of this substance may cause a coagulopathy 4. Our results give further evidence to the theory that this substance is partially clotted by showing there are altered levels of new specific hemostasis markers in MSB. We found high concentrations of the platelet specific released products Pf4 and BTG in MSB indicating platelets were activated. FPA, FDP, and D-dimer were elevated suggesting fibrin formation and degradation were accelerated in MSB. Antithrombin III was low in MSB suggesting high concentrations of activated thrombin were present. Further investigation using these new specific hemostasis markers on a larger patient population with a control group will be done to determine if autotransfusion with MSB could contribute to the development of a coagulopathy in the postoperative period following cardiac surgery.

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Title: ELECTROCARDIOGRAPHIC PLACEMENT OF A MULTIORIFICE CENTRAL VENOUS CATHETER

Authors: JJ Marshall, M.D., JL Orth, KW Smith, M.D., JL Peters, M.D., WL Hastings, B.S.

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Introduction. Multiorifice catheters have been shown in vitro (1) and in vivo (2) to be superior to single orifice catheters in retrieving air emboli. Proper positioning with the most proximal orifice 1 to 3 cm proximal to the junction of the superior vena cava (SVC) and the right atrium (RA) is essential to obtain the greatest percentage of air retrieval (1). Single orifice catheters can be placed accurately by using the catheter as an electrode in a bipolar ECG lead (3). Studies using the multiorifice catheter as an electrode in a bipolar lead are lacking. This study was designed to determine whether a multiorifice catheter (Arrow multiorifice 85-cm 16-gauge catheter) can be placed accurately by using the catheter as an intravascular electrode.

Methods. Four mongrel dogs weighing 25 to 30 kg were anesthetized with halothane 1 to 2% in oxygen. A short introducer (3 to 5 cm) was inserted into the right external jugular vein. A right thoracotomy was performed so that the SVC-RA junction could be visualized and palpated. The multiorifice catheter was marked in centimeter increments from the tip. This catheter has 5 orifices - one at the tip and 4 side orifices. The first side orifice is 1.2 cm from the tip and the other orifices are located proximally at 0.5-cm increments up the catheter. A similar catheter was cut just proximal to the first side orifice, making it a single orifice catheter. An Arrow-Johans intravascular ECG adapter was placed proximal to the catheter hub and this was connected to a saline-filled IV infusion set. The left leg electrode connection was placed on the adapter and the ECG recorder was set on LEAD II. Paper speed was 25 mm/second and calibration was 0.5 my/cm. The catheter was advanced through the sheath in 1-cm increments and the ECG recorded. This was done for both the multiorifice and the single orifice catheters. The distance from the SVC-RA junction was determined by palpating the tip of the catheter through the thoracotomy at the SVC-RA junction. Negative numbers refer to positions in the SVC proximal to the SVC-RA junction. Positive numbers refer to positions in the RA distal to the SVC-RA junction.

Results. The intravascular ECG differed markedly between the multiorifice and the single orifice catheters. The single orifice catheter resulted in the follwoing ECG trace: negative deflection of P wave and QRS in the SVC, P wave amplitude exceeded the QRS amplitude somewhere between -2 and +2 cm from the SVC-RA junction, P wave became biphasic with an upward/downward deflection ratio of at least .16 at either +2 or +3 cm from the SVC-RA junction. The multiorifice catheter resulted in the following ECG trace: negative deflection P and QRS in the

SVC, P wave amplitude never exceeded QRS amplitude, P wave never became biphasic, P wave reached maximum amplitude (negative deflection) on the average at +1 cm from the SVC-RA junction. The figure shows the P wave amplitude/maximum P wave amplitude plotted against the distance from the SVC-RA junction. The amplitude peaks at +1 and remains high for several cm past the juction of the SVC-RA. Therefore, the optimal position for this multiorifice catheter is obtained by advancing it until maximum P wave amplitude and withdrawing 1 to 2 cm, thereby placing the most proximal port 1 to 3 cm proximal to the SVC-RA junction.

Discussion. This study indicates that a multiorifice catheter can be placed accurately by using an intravascular ECG. The optimal position of the multiorifice catheter depends somewhat on the design. The most proximal orifice aspirates most effectively (has the largest negative pressure) and therefore it should be 1 to 3 cm above the SVC-RA junction. If the orifice location varies significantly from the catheter used in this study, not only may the ECG be different, but the multiorifice catheter may have to be withdrawn more or even advanced to locate the most proximal orifice 1 to 3 cm above the SVC-RA junction. This contrasts with the placement of a single orifice catheter where the catheter is usually pulled back several cm from where a biphasic P wave is obtained. This study demonstrates that in dogs the placement to the most effective position for a single orifice or a multiorifice catheter by intravascular ECG differs considerably.

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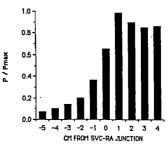


Fig. 1

Title: ASPIRATION FLOW RATE DETERMINES AIR FEIRIEVED AFTER VENOUS AIR EMBOLISM IN DOGS

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Introduction. Placement of a central venous catheter for aspiration of venous air emboli is important in patients at high risk for entrainment of large amounts of air. The use of a multiorifice catheter has been shown to be superior to a single orifice catheter in an in-vitro model of the right heart. In dogs, a nultiorifice catheter was also shown to be superior to a single orifice catheter in both percentage of air retrieved as well as incidence of successful resuscitation. The most effective position for a multiorifice catheter appears to place the most proximal orifice 1 to 3 cm above the superior vena cava-right atrium (SVC-RA) junction. Several multiorifice catheters are available which differ in lumen area, length, orifice pattern and site of orifice placement. To our knowledge, no study has determined how to ispirate such a catheter. Therefore, this study was undertaken to determine what range of flow tates is necessary to retrieve significant amounts of a bolus air embolus and how long these flow rates need to be applied. Although a large syringe can generate an appreciable amount of negative pressure and thus flows, it is impractical in that it ties up the mesthesiologist and has a limited volume. The modalities studied were a variable-speed roller oump and a vacuum bottle.

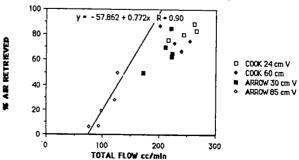
Methods. Six mongrel dogs weighing 25 to 10 kg were anesthetized with halothane in oxygen and pancuronium. A right-sided thoracotomy was erformed and the air aspiration catheter was nserted via the right internal jugular vein so that the tip of the catheter was palpable at the WC-RA junction. This distance was measured and ill subsequent catheters were placed to the same epth. The animals were instrumented with a ulmonary artery catheter and an aortic pressure atheter. The animals were inclined to 45 egrees by means of a specially built table. ir was injected as a 2 mL/kg bolus over 20 econds into a forelimb intravenous line. spiration through the central catheter was egun 5 seconds after the air injection tarted. Three aspiration modalities were ested for each catheter. A variable-speed oller pump with flow rates of approximately 150 nd 250 cc/min (measured through the connecting ubing without a catheter) and a vacuum bottle approximate negative pressure -20 inches of Hg nd flow rate of 250 cc/min) were used. spirations were continued for 1 minute and all ir was collected in a bubble trap. The time eriod from the start of aspiration until no ore air could be aspirated (only an occasional ubble was seen in the tubing) was recorded. our multiorifice catheters were tested: Arrow 5-cm 16-gauge, Arrow 30-cm 16-gauge, Cook 60-cm 4-gauge, Cook 24-cm 14-gauge. Total flow was alculated as air plus blood aspirated.

Results. The percentage of air retrieved sing the roller pump was linearly related to

the total flow with an R value of 0.92. The calculated flows for 25, 50, and 75% air retrieval are 121, 167, and 212 cc/minute respectively. The Arrow 85-cm catheter, which only allowed flows of approximately 100 cc/min, consistently aspirated less air. The other three catheters allowed comparable flows with the different modalities and consequently aspirated similar amounts of air. The percentage of air retrieved was also linearly related to the total flow achieved with the vacuum bottle with an R value of 0.90 (Figure 1). The calculated flows for 25, 50, and 75% air retrieval are 108, 140, and 173 respectively. The time until no air was retrieved was less than 45 seconds in all cases.

Discussion. This study demonstrates that the percentage of air retrieved is linearly related to the flow generated through the catheter. Seventy to 90% of the air could be retrieved with flow rates of approximately 225 cc/minute by either the roller pump or the vacuum bottle. Flows of approximately 100 cc/minute resulted in only 10 to 20% of air retrieved. This can be explained by the fact that virtually all of the air is aspirated by 45 seconds so that high flows for a short time are needed. The vacuum bottle out-performed the roller pump probably because of a faster response time in that the roller pump took several seconds to reach peak flows once activated. Under the conditions of this study, which attempted to simulate life-threatening bolus air embolus in 45-degree upright dogs, the following conclusions can be reached: 1) A catheter and an aspiration system which will generate flows of at least 200 cc/minute are desirable. Therefore, the resistance of a catheter and retrieval system must be critically analyzed. 2) Response time is very important as air is either aspirated or passes through the heart very rapidly. 3) The hole pattern of a multiorifice catheter may not be as important as the flow characteristics (i.e., the resistance) of the catheter.

AIR RETRIEVED VS FLOW (vacum bottle)



Title: MOLECULAR MECHANISM FOR HALOTHANE-INDUCED &-ADRENERGIC HYPORESPONSIVENESS IN VITRO

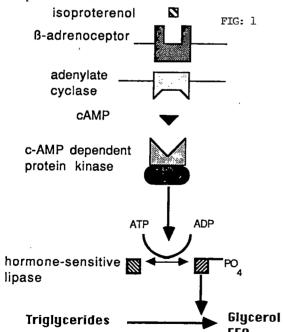
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Introduction. Halothane attenuates adrenergic responsiveness by inhibiting ganglionic transmission and norepinephrine release from the postganglionic presynaptic nerve terminals. Additionally, halothane may affect adrenergic responses at the postsynaptic effector cell although the direction and extent of these changes is controversial. Since coinciding presynaptic effects may be confounding variable in the interpretation of the conflicting data, we have used the isolated rat adipocyte as a model in which to test halothane's postsynaptic effects on adrenergic responses(Fig 1). When ß-adrenergic receptors are occupied by agonists such as isoproterenol, they activate adenylate cyclase. This catalyzes the conversion of ATP into cAMF which binds to the regulatory component of cAMP-dependent protein-kinase, releasing catalytic unit that activates hormone-sensitive lipase by phosphorylation. Previously demonstrated that halothane inhibited £-stimulated lipolysis by an action at a site distal to the cAMP-dependent protein kinase step (Fig 1). By examining subsequent steps in the biochemical cascade, we now report on the molecular mechanism whereby halothane produces &-adrenergic hyporesponsiveness.



Methods. The effect of halothane (2.5%v/v in $0_2/C0_2$), on the lipolytic response (nmol of glycerol released/ 10^5 rat adipocytes/h) to isoproterenol stimulation, 10^{-6}M was assessed at concentrations known to result in the maximal inhibitory and stimulatory effects¹. Cyclic AMP-dependent protein kinase (A-kinase) activity and hormone-sensitive lipase activity were assayed at the same isoproterenol and halothane concentrations. Also, to determine whether halothane affected enzyme assays directly, the catalytic activities from

unexposed cells were also measured with halothane in the assay medium ("broken cell preparation"). For all experiments, control exposures $(0_2/\text{CO}_2)$ were performed in parallel and assays were performed in triplicate. Paired t-test was used to compare data with and without halothane exposure. Statistically significant differences existed when the P value was <0.05. Data are expressed as means $\pm \text{SEM}$ of 4 separate experiments unless otherwise indicated.

Results. The addition of halothane did not change isoproterenol-stimulated A-kinase activity ratio (0.62±0.04 vs 0.60±0.05). Isoproterenol (□), increased the activity of hormone-sensitive lipase four-fold above the basal levels (▲) in the control cells (Fig 2). However when cells were exposed to halothane in the presence of isoproterenol (♣), the stimulation of hormone-sensitive lipase was attenuated by 70% (Fig 2). Halothane had no direct inhibitory effect on the isoproterenol-stimulated activity of hormone-sensitive lipase in the broken cell preparation.

Discussion. Halothane, dose-dependently and inhibits isoproterenol-stimulated reversibly, glycerol release in isolated adipocytes1. present study we have found that halothane did not prevent the activation of A-kinase by isoproterenol nor did it impair A-kinase activity. However, there was a marked inhibition in isoproterenol's ability to activate hormone-sensitive lipase enzyme activity during halothane exposure (Fig 2) which was not present under broken cell conditions. Our data suggest that halothane markedly attenuates the activation of hormone-sensitive triglyceride lipase activity (Fig 1) in the presence of appropriately activated A-kinase (the protein phosphorylating enzyme). It is conceivable that many of halothane's pharmacologic properties in other systems, (e.g. negative inctropy in the heart) may be explained in part by its ability to attenuate phosphorylation and thus activation of regulatory proteins (e.g. voltage-sensitive calcium channels).

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[itle:

EFFECT OF ANESTHESIA INDUCTION IN THE RELATION BETWEEN ELECTRICAL AND ELECTROMECHANICAL

SYSTOLE AND DIASTOLIC TIME

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<u>Introduction</u>. The duration of electrical systole (QT) is shorter and parallels the electromechanical systole (QS₂) throughout the esting heart rate (HR) in normals. Reverse of the formal QT \leq QS₂ relationship constitutes a major risk for sudden death in patients with coronary artery lisease (CAD) (1).

The greatest proportion of coronary flow occurs in diastole and subendocardial flow is totally liastolic particularly in patients with CAD and eft ventricular hypertrophy (2,3).

Studies have shown that increased adrenergic activity and/or pharmacologic agents may alter the formal QT-QS, relationship and the diastolic time subendocardial perfusion time) (2,3).

The effect of anesthesia induction on QT-QS, elationship and diastolic time (DT) have not been horoughly evaluated. The present study was ndertaken to investigate the change in QT-QS, elationship and DT during anesthesia induction in atients undergoing elective surgical procedures ith a normal cardiovascular system.

Methods. Eleven ASA I-II patients aged 17-55 31.6±11.5) were studied. All patients were prexygenated with 100% oxygen before the anesthesia nduction with thiopental 6 mg/kg and uccinylcholine 1 mg/kg. Following adequate muscle elaxation, the trachea was intubated. Anesthesia aintenance consisted of a 70/30% mixture of itrous oxide/oxygen with 2-3% Isoflurane.

Electrocardiogram and phonocardiogram were ecorded continuously on FM tape. The QT, QS, and T (cardiac cycle (RR) minus QS,) were measured rom the recordings at the following times: reinduction, after thiopental, after uccinylcholine, after intubation, and every three inutes for nine minutes. Five to 10 cardiac ycles were averaged at each time to minimize espiratory variations. Blood pressure was easured by oscillometry. Statistical evaluation as performed using analysis of variance with epeated measures.

Results. The normal $OT \le OS_2$ relationship eversed $(OT > OS_2)$ in all patients sometime during he anesthesia induction (p < 0.0001). DT/sec and T/min decreased significantly (p < 0.0001). HR and lood pressure increased during anesthesia nduction (see Table).

Discussion. Our results demonstrate that significant changes occur in QT-QS₂ relationship and DT during anesthesia induction in patients without cardiovascular disease. The decrease in diastolic time may compromise subendocardial perfusion in patients with CAD and/or left ventricular hypertrophy (2.3). The abnormal QT-QS₂ relationship (QT>QS₂) may result in ventricular arrhythmia in patients with electrical instability (1). This study provides the basis to compare other types of anesthesia induction in patients without cardiovascular disease and/or with pathologic states.

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				TIME*	,	
PARAMETER	_1_		_3_	4	_5_	_6_
QT-QS2	-28.09	-20.08	-7.80	12.48	8.98	-20.59
msec	<u>+</u> 18.33	±10.32	<u>+</u> 7.37	±16.06	<u>±</u> 16.09	±10.45
DT/sec msec	<u>+</u> 162:37	±157:92	268.40 ±80.03	198.21 ±30.05	203.72 ±15.82	244.61 ±53.87
DT/min	30.64	27.81	24.79	21.81	23.37	23.46
sec	<u>+</u> 4.69	±5.38	±3.29	±2.26	±5.25	<u>1</u> 2.99
HR	73.54	84.76	95.58	110.93	115.04	97.91
beats/min	±17.27	±19.22	±12.61	±7.11	±25.83	+10.71

^{*1=}preinduction
2=thiopental
3=succinylcholine
4=intubation
5=3 minutes from thiopental
6=9 minutes from thiopental

NALBUPHINE ANTAGONIZED FENTANYL-INDUCED ANALGESIC AND CARDIORESPIRATORY EFFECTS IN THE SAME DOSE RANGE IN DOGS

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Introduction. Nalbuphine, a mixed agonist/ant-agonist opioid, is said to antagonize the respiratory depressant but less so the analgesic effects of fentanyl. To determine if nalbuphine were to antagonize fentanyl's cardiorespiratory and analgesic effects at different doses, we studied dose/effect relations in unanesthetized dogs in whom a maximally effective concentration of fentanyl in the cerebroventricular system was maintained by continuous perfusion.

Methods. Seven experiments were performed on five unanesthetized beagle dogs in whom stainless steel cannula, one in a lateral ventricle and the other in the cisterna cerebello-medullaris, had been implanted for cerebroventricular perfusion with fentanyl in previous operations (1). The following variables were recorded: heart rate, arterial blood pressure, respiratory rate, arterial blood gas tensions, and pH. To test for analgesia, increases in heart rate and blood pressure in response to tail clamping with a hemostat were used.

While maximally effective intraventricular concentrations of fentanyl (50 μ g/ml, flow rate 0.1 ml/min) were maintained throughout the course of the experiments, increasing amounts of i.v. nalbuphine were injected in 5 min intervals (25, 50, 100, 200, 500, and 1000 to a total of 1875 μ g/kg within 30 min) to antagonize the fentanyl-induced effects.

Results. The fentanyl-induced cardiorespiratory and analgesic effects all were antagonized by nalbuphine in the same dose range (Fig. 1). Cerebroventricular perfusion of fentanyl elicited a marked fall in heart and respiratory rate with signs of alveolar hypoventilation, unresponsiveness to tail clamping, and sleep-like behaviour in all dogs. In spite of continued intraventricular fentanyl concentration, nalbuphine reversed all these effects in a dose-related fashion. In fact, all animals woke up, showed normal cardiovascular response to tail clamping, and resumed normal cardiorespiratory function after the fifth dose, i.e. after a total dose of 1875 µg/kg nalbuphine.

Discussion. With the cerebroventricular perfusion protocol employed here, fentanyl produced the same cardiorespiratory and analgesic effects as maximally effective doses after intravenous injection in awake dogs (2). Since nalbuphine reversed the fentanyl-induced cardiorespiratory and also the analgesic effects in the same dose range, it is apparantly impossible to reverse with nalbuphine fentanyl's unwanted cardiorespiratory depressant effects but to maintain its analgesic action. Thus, nalbuphine, in agreement with previous experiments (3) exhibits merely opiate antagonist rather than agonist properties in dogs.

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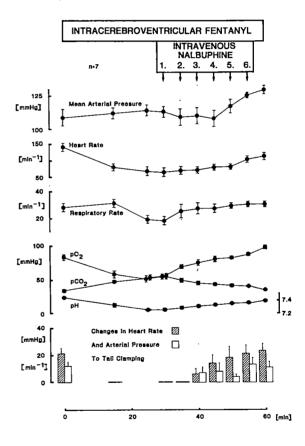


Fig. 1
Agonist action of intravenous nalbuphine on fentanylinduced cardiorespiratory and analgesic effects in
unanesthetized dogs.

Note, in the presence of maximally effective intracerebroventricular concentrations of fentanyl, nalbuphine reverses all fentanyl-induced effects in the same dose range. $\hbox{D-ALA}2-\hbox{D-LEU}^5-\hbox{ENKEPHALIN INDUCED CARDIORESPIRATORS} \hbox{ $ANALGESIC EFFECTS RESEMBLE THOSE OF OPIOID $mu-AGONISTS$}$ IN \$AWAKE DOGS

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Introduction. D-Ala²-D-Leu⁵-Enkephalin (DADL) is an opioid peptide with preferential affinity to opiate receptors of the delta-type. In awake dogs, intrathecally applied DADL produced naloxone-reversible analgesia and respiratory depression, but no cardiovascular effects¹. Because of its poor lipophilicity, this agent has been advocated for intrathecal administration for the treatment of intractable pain²,³,⁴. In view of the potential risk of a cephalad spread it appeared to be of interest to study the effects of intraventricularly applied DADL.

Methods. In 6 experiments on awake dogs, DADL was perfused continuously in increasing concentrations (5-200 µg/ml at a flow rate of 0.1 ml/min) through the cerebroventricular system via chronically implanted steel cannula (ore in a lateral ventricle the other in the cisterna cerebello-medullaris). The rardiovascular (heart rate, arterial blood pressure), respiratory (respiratory rate, arterial blood gas tensions and pH) and also analgesic and behavioural effects (response to tail clamping) were monitored.

while the intraventricular concentration of DADL was maintained constant, antagonization was attempted with either naloxone (doses from 25 - 800 µg given intravenously every 5 minutes) or with the delta-selective antagonist ICI 154129 (perfused through the cerebroventricular system, concentration range 5 - 5000 µg/ml).

Results. Intraventricularly applied DADL proluced a concentration-related bradycardia with a slight increase in arterial blood pressure and respiratory slowing with signs of alveolar hypoventilation (increase in PaCO₂ and decrease in pH and PaO₃) (Fig. 1). All animals showed sleep-like behaniour, and were rendered unresponsive to painful stimulation at intraventricular DADL-concentrations of 200 µg/ml (Fig. 2). All of these effects were reversed by naloxone in a dose-related fashion, where—us ICI 154129 was ineffective.

Discussion. DADL, when perfused through the ntracerebroventricular system produces cardiorespiatory slowing with alveolar hypoventilation, sleeplike behaviour and analgesia in awake dogs. This attern resembles that of other opioids with high affinity for mu-binding sites, particularly that of entanyl⁵. Since all effects of DADL are promptly regreed by naloxone, but not by the delta-selective ntagonist ICI 154129, we suggest that DADL much like the classical opiates acts at opiate receptors of the mu-type.

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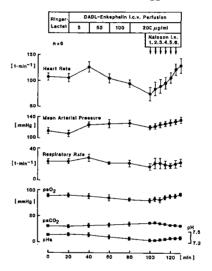


Fig. 1 Cardiorespiratory effects of increasing intracerebroventricular concentrations of DADL. Naloxone was injected intravenously at increasing doses (25, 50, 100, 200, 400, and 800 μg) every 5 minutes.

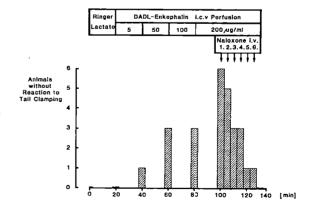


Fig. 2 Number of animals unresponsive to painful stimulation by increasing intracerebroventricular concentrations of DADL. Dose-related antagonism by increasing amlunts of i.v. naloxone (25, 50, 100, 200, 400, and 800 μ g).

Title: Authors: Affiliations: LUMBAR EPIDURAL ANALGESIA POST-THORACIC SURGERY J. Melendez, M.D., V. Cirella, M.D., T. Dodds, M.D. Columbia University Department of Anesthesiology, Columbia-Presbyterian Medical Center and College of Physicians and Surgeons 630 West 168th Street, New York, New York 10032

Introduction: Epidural fentanyl has been successfully used for post-operative analgesia in patients undergoing thoracic surgery. Due to the high lipid solubility and rapid tissue uptake of fentanyl, the risk of rostral spread and delayed respiratory depression is reduced by comparison with that following the use of morphine. It has been stressed that in order to be effective in thoracotomy patients, the drug must be administered into the thoracic epidural space proximally to the level of the incision. Previous studies of lumbar epidural fentanyl have suggested increased spread of analgesia by increasing dosage and volume of drug administered. The thoracic placement of a epidural catheter is more difficult and potentially more dangerous than insertion into the lumbar epidural space. We, therefore, investigated the feasibility of injecting a high dosage/high volume of fentanyl into the lumbar epidural space to improve rostral spread and achieve adequate thoracic analgesia.

Methods: All patients undergoing elective thoracotomies and median sternotomies for non-cardiac surgery within a four month period were included. All were premedicated with MS .1 mg/kg IM, Promethazine 0.5-1.0 mg/kg IM and Glycopyrolate .2-.3 IM. Upon arrival to the operating room, EKG, BP cuff, foley catheter, intravenous, and arterial lines were inserted. An epidural catheter was placed at the third or fourth lumbar intervertebral space. Proper placement of catheter was ascertained using Lidocaine 1.5% with epinephrine 1:200,000. General anesthesia was induced with Pentothal 5 mg/kg and Vecuronium .15 mg/kg (only on thoracotomies), and naintained with Forane/N₂O/O₂. No narcotic was administered during surgery. Thirty minutes prior to the conclusion of anesthesia, fentanyl 200 ug in 16 cc NS (total volume 20 cc) was administered via the epidural catheter. All patients were transerred to the ICU. Supplemental oxygen was administered and respiratory rates were monitored by the nursing staff. Upon complaint of pain, which was rated by the patients on a scale of 0 to 10 (0 = no pain, 10 = severe pain) additional dose of fentanyl 200 ug/NS 16 cc were injected epidurally and pain scores attained 30 minutes thereafter. Interval between all epidural doses were recorded. Arterial blood gases were determined pre-injection and at 30 minutes after the administration of each epidural dose. Catheters were removed prior to discharge from the ICU or after documentation of migration out of the epidural space. Data were analyzed using Student's t-test and Mann-Whitney Test. All results were expressed as mean + SD. Null hypothesis was rejected at p 0.05. All thoracotomies were performed at either T4 or T5 interspace. Fentanyl dosing interval, pain scores and resting ${\tt pCO}_2$ are shown.

Results: Seventeen patients, nine males and eight females were studied so far. Their age ranged from 18 to 73 years.

Procedures included lobectomies, pneumonectomies, pleauradeses and thymectomies.

Fentanyl Dosing Interval	3.8 + 1.4 hrs.
Resting pCO2 Pre-injection	40 + 7 mm Hg
Post	41 + 5 mm Hg
Duration of catheter placement	26 + 12 hours
First Dosage Interval	3.7 + 1.5 hrs.
Last Dosage Interval	$5.0 \pm 3.5 \text{ hrs.}$

Percent of Patients With Pain Score

Pain Score 0 1 2 3 4 5 6 7 8 9 10

Pre-injection 7 7 15 32 11 29

Post-injection* 12 23 47 13

*Significantly different from pre-injection scores

All patients experienced pain relief within 15 minutes after fentanyl administration. Although sommolent after each dose, they were easily arousable and behaved appropriately at all times. There was no incidence of significant respiratory depression and hypercarbia. In fact, one patient who had undergone a pneumonectomy, was found to have pCO₂ decreased from 57 to 43 mmHG after injection. This was attributed to an improvement of ventilation with pain relief. No statistically significant difference between dosage intervals could be elicited from the data. One episode of nausea, not requiring treatment, was recorded. Vomitting and pruritis were absent in our population. Foley catheters made it impossible to assess urinary retention.

Conclusion: Adequate analgesia was achieved in all postthoracotomy/sternotomy patients studied by injecting fentanyl 200 ug in a 20 ml volume. This high dosage/high volume technique resulted in sufficient rostral spread to provide adequate anagesia to our population. The rapid onset and moderate duration of action were in agreement studies involving abdominal procedures. Theoretically, high volume/high dosage techniques might be associated with an increased evidence of side effects. This was not the case in our study. No patient experienced significant respiratory depression, vomiting or puritis. We propose the use of this technique as a safe, practical alternative to thoracic epidural analgesia for postoperative pain relief in patients undergoing thoracic surgery.

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Title:

NONCARDIAC SURGERY IN HEART TRANSPLANT RECIPIENTS IN THE CYCLOSPORINE ERA

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Introduction. Non cardiac surgery in heart transplant recipients is becoming increasingly common due to the improved results and increasing frequency of cadia transplantation. The introduction of cyclosporine in immunosuppression at our institution in March 1983 has improved graft survival and decreased the amount of intercurrent infection in these patients. Recently animal studies have suggested an increased duration of action of barbiturates and possibly narcotics after an acute dose of cyclosporine (1). The response of patients maintained on chronic immunosuppressive therapy with cyclosporine to general and regional anothesia has not been widel documented.

Methods. Twenty-eight of 124 heart transplanrecipients grafted since March 1983 at our institution underwent 35 noncardiac operative procedures after transplantation. We have retrospectively reviewed their anesthetic management in an attempt to define optimal anesthetic technique for this group of patients and to determine if chronic cyclosperine therapy has any effecon the course and duration of anesthesia.

Results. The noncardiac surgical procedures requiring anesthesia are listed in Table I. Operations in all patients were performed between 4 months and 4 years after transplantation. All patients were chronically maintainec on cyclosporine and steroids for immunosuppression. Cyclosporine levels were followed weekly; endomyocardia! biopsies are performed regularly. At the time of operation all patients had therapeutic levels of cyclosporine. Doses of cyclosporine were maintained perioperatively via an oral or NG route. All patients received stress doses of steroids perioperatively. Sterile precautions were naintained. No patient was acutely rejecting at the time of surgery. Monitoring in all patients included EKG, BP by scillometric technique, esophageal stethescope, emperature, pulse oximetry and end tidal CO₂. One patient who underwent resection of a thoracic aortic neurysm had a Swan Ganz catheter placed. Two of the hirty five procedures, a hernia repair and drainage of a high abscess were performed under spinal anesthesia using etracaine. The calculated dose of tetracaine was based on patient height and location of the surgery. In both cases the dose provided excellent motor and sensory ·lockade. Both blood pressure and heart rate were onstant following the onset of anesthesia. Anesthetic luration was within normal limits. No complications ccurred.The remaining thirty three procedures were erformed under general anesthesia. Two inhalation nductions with Halothane/N₂0/O₂ were performed in one ive year old child for lymph node biopsy and erniorrhaphy. Up to 2.5% Halothane/70% N₂0/30% O₂ rrhythmias. Intravenous inductions with barbiturate, arbiturate and narcotic or benzodiazepines were equally ffective. The amount of thiopental necessary to produce nconsciousness was 5-6 mg/kg in most patients. When arcotic (fentanyl 2ug/kg) was used as an induction agent ith thiopental the dose was reduced to 3-4 mg/kg. The atients also required normal benzodiazepine doses to roduce unconsciousness. In six patients anesthesia was variationed with narcotic, relaxant and N_2O/O_2 . 70% 20/30% O₂ was used in all these cases. Narcotic equirements were essentially normal, fentanyl 5-8

ua/ka/hour. Relaxants were used in routine doses. Isoflorane was the sole potent agent used with 70% N20 30%/O₂ in those patients maintained with inhalation agents. All patients received 5-1% isoflorane during the majority of anesthetic time. Muscle relaxation was achieved with either metubine (.2-.3 mg/kg) or vecuronium (.08 mg/kg) with neuromuscular block monitoring. All patients were easily reversed at the termination of surgery with a single dose of neostigmine 2.5 mg and glycopyrrolate 0.6 mg intravenously. Extubation was accomplished easily in the operating room. There were no immediate post operative complications. Hemodynamic stability is apparent in all anesthetic records. Heart rate remained between 90-105 bpm as is expected in the denervated heart. Blood pressure showed little variability in the group and remained between 100-150 systolic in all cases. There were also very few variations greater than 10-15 mmHg within an individual's record. In particular there was often no sympathetic response to either intubation or incision. Fluid requirements were appropriate for the type of surgery. Sleep time was not prolonged in the immediate post operative period. Discharge from the recovery room was prompt in all cases.

Discussion. A normal range of doses of intravenous agents, muscle relaxants, inhalation agents and local anesthetics provide effective anesthesia for noncardiac surgical procedures in patients after cardiac transplantation on chronic cyclosporine therapy. interactions between anesthetic agents, in particular barbiturates and narcotics and cyclosporine have been described in animal models (1). An acute dose of cyclosporine seems to increase sleep time and duration of anesthesia. In the clinical setting of a patient population chronically maintained on cyclosporine this does not seem to be the case. The small range of variability in both heart rate and blood pressure in each individual patient may make anesthetic depth difficult to determine intraoperatively.

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Table 1. Procedures Performed	., .,
Pacemaker Insertion	3
Open Long Resection	2
Sternal Resection for Infection	1
Mediastinal Drainage for Infection	i
Pleural Abrasion	i
Thoracic Aortic Aneurysm Resection	i
Exploratory Laparotomy	Í
Iliac Artery Repair	i
Cholecystectomy	8
Drainage For Rectal Abcess	Ī
Herniorraphy	2
Repair of Vental Hernia	1
Cataract Surgery	3
Lymph Node Biopsy	Ī
Resection Aspergilloma Thigh	i
Resection Posterior Thigh Mass	i
Therapeutic Abortion	1
Bilateral Hip Replacement	i
Bilateral Core Reversal Femeral Head	ż
Arthroscopy	2

Title: DOSE RESPONSE OF MIVACURIUM IN PEDIATRIC PATIENTS

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Introduction. Mivacurium (BW B1090U) is a new nondepolarizing muscle relaxant whose safety and efficacy has been demonstrated in adults (1). It is characterized by a short duration of action and lack of cumulative effects (2). The current study was undertaken to evaluate the safety and the dose response relationship of mivacurium in pediatric patients.

Methods. The protocol was approved by the Subcommittee on Human Studies, Committee of Research, and by the Pharmacy Committee of our institution. Written informed consent was obtained from parents and from children seven years of age and older.

Twenty-six ASA I & II children between the ages of two and twelve years were studied. Children less than 7 years were premedicated with rectal methohexital (20-40 mg/kg); older children did not receive any medication. The electrocardiogram, heart rate, blood pressure, precordial sounds, oxygen saturation, end-tidal CO2, and temperature were routinely monitored. Supramaximal train-of-four (2 Hz for 2 sec) stimili were applied at a frequency of 0.1 Hz. The adductor pollicis contraction in response to stimilation of the ulnar nerve was recorded on a Grass polygraph with a force displacement transducer (Grass FT-O3).

General anesthesia was induced with nitrous oxide, oxygen, and halothane, and maintained with 1.0-1.25% inspired halothane, nitrous oxide and oxygen (2:1 ratio). Following stabilization of the twitch response each patient received a single bolus dose of 0.02, 0.04, 0.05 or 0.06 mg/kg of mivacurium intraveously; the maximum neuromuscular depression after these doses was recorded. The vital signs were also ascertained; blood pressure and heart rate were measured at baseline, every minute for the first five minutes, and every two minutes for the following ten minutes, then routinely every five minutes. Surgical stimulation was minimal during the first ten minutes. Five minutes after the initial dose of mivacurium when the maximum neuromuscular depression was obtained from the initial dose, an additional dose of 0.1 mg/kg of mivacurium was administered. Thereafter endotracheal intubation was performed.

If residual neuromscular relaxation was present at the completion of the surgical procedure, atropine (0.03 mg/kg) and edrophonium (0.6 mg/kg) were administered.

Results. The mean $(\pm s.E.)$ age of the study group was $5.8(\pm 0.8)$ years and the mean weight was $23.0(\pm 2.9)$ kg. Based on adult studies, we had expected that 0.02 mg/kg of BW 1090U would provide about 25% depression of the twitch response. However, after evaluating three children, we found that this dose did not achieve any significant neuromuscular depression. Therefore the initial dose was increased to 0.04 mg/kg. Consequently the

remaining five patients in this group received 0.04 mg/kg mivacurium that achieved 30(±10)% depression of the first twitch of the train of four (T1). The following nine patients received 0.05 mg/kg of mivacurium that produced 53(±9.1)% depression of T1. In the last nine patients 0.06 mg/kg produced 68.2(±9.2)% depression of T1. The suppression of twitch response was positively correlated with the dose of mivacurium. The dose response relation was calculated from the depression of the initial T1 component of the train-of-four response from the dose of mivacurium. The calculated ED₂₅ for mivacurium were 0.039, 0.051, 0.095 mg/kg respectively. The slope of the dose response curve was 1.47.

The subsequent dose of 0.1 mg/kg produced $98.9(\pm1.3)\%$ suppression up to T1 within $1.3(\pm0.2)$ min of its administration. Following this dose the time to recovery from injection of the drug to 5% of control twitch height occurred in $5.9(\pm0.6)$ min, to 25% control in $7.5(\pm0.5)$ min, and to 95% of control in $14.1(\pm1.1)$ min.

<u>Discussion and conclusion</u>. Mivacurium is a short-acting nondepolarizing muscle relaxant with an ED_{50} of 0.051 and ED_{95} of 0.095 mg/kg. Compared to adult data of mivacurium (3), children seem to require larger doses of mivacurium on a mg/kg basis to achieve comparable degrees of neuromuscular depression.

Mivacurium has an intermediate potency between atracurium and vecuronium, but has a significantly shorter duration than both of them (4,5). Considering the non-depolarizing nature of mivacurium and its short duration of action this drug may be valuable for short surgical procedures in children.

The suppression of twitch response was positively correlated with dose of mivacurium

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A COMPARISON OF AUDITORY EVOKED POTERTIALS AND PSYCHOMOTOR TESTING FOR ASSESSING RECOVERY FROM Title:

MIDAZOLAM SEDATION

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Introduction Evoked potentials, EEG changes produced by auditory, visual or sensory stimulaticr, have been used to assess the depth of anesthesia 1 but their use in assessing recovery from anesthetic or sedative drugs has not been investigated. A previous study in our department using a double blind, placebo controlled design, demonstrated that the amplitude of P_{300} , a positive wave occurring 300 ms after an auditory stimulus, was significantly reduced following the oral administration of midazolam 15 mg (2). The present study was therefore undertaken to investigate in detail the use of P300 amplitude in measuring recovery from midazolam sedation and to compare it with standard psychomotor techniques.

Following University Medical Ethical Methods Research Committee approval 8 healthy, fasting mal= volunteers who had given informed verbal consent were recruited into the study. Scalp electrodes were attached and baseline auditory evoked potentials (AEP's) recorded from midline sites referred to linked mastoids. Psychomotor testing, consisting of 4-choice reaction times (CRT's) and critical flicker frequency threshold (CFFT's) was also carried out, the subjects having undergone a minimum of 20 practice sessions beforehand to reduce practice effects. Midazolam 0.3 mg kg⁻¹ was then infused intravenously at 1 mg min⁻¹ and AEP, CRT and CFFT measured at hourly intervals for the next 5 hr. Midazolam concentrations were estimated using GLC on blood samples taken immediately prior to each test session.

Results The results are summarised in Table 1. Their analysis showed that P300 amplitude was initially greatly reduced but recovered in a time dependent fashion, regaining baseline levels approximately 6 hr after the start of the infusion. The results for the CRT and CFFT were similar, both of these also achieved baseline levels at 6 hr. The blood midazolam concentrations were highly correlated (Pitman rho correlation) with P300 amplitude (r = 0.81, p < 0.001). Analysis of individual results showed that this correlation was significant for all patients (p < 0.05). This analysis was repeated for both the CRT's and CFFT's and similar degrees of correlation were obtained.

Discussion All three methods of assessing recovery achieved baseline levels at approximately the same time and showed the same high degree of correlation with blood midazolam levels demonstrating that they are of similar sensitivity in measuring recovery from benzodiazepine sedation. In all subjects the clinical impression was that all volunteers were fully recovered by the end of 6 hr period suggesting that the tests produce clinically relevant results.

As an index of recovery evoked potential measurement has theoretical attractions: it is objective, in some circumstances can be measured without the need for the subject's active co-operation and is not subject to practice effects. Practice effects, a major disadvantage of psychomotor testing, were largely eliminated by our study design but the repetitive testing required to do this may not be practical in the clinical situation. The results show that P300 amplitude provides a sensitive and accurate measure of recovery but in these circumstances had no advantages over the much simpler CRT and CFFT measurements and at this stage cannot be recommended as a superior alternative.

Table 1 Mean (+ SD) blood midazolam levels, AEP's, CRT's and CFFT's.

Time (hr)	Blood levels (ng ml ⁻¹)	AEP (μV)	CRT (ms)	CFFT (Hz)
0	750 + 52	-11.3 <u>+</u> 3.64	408 ± 52 951 +325	26.4 <u>+</u> 5.27 13.4+0.79
2	259 <u>+</u> 52 176 <u>+</u> 64	-2.8 <u>+</u> 1.06 -4.7 <u>+</u> 4.11	758 <u>+</u> 274	18.8+2.50
3 4	127 <u>+</u> 54 90 + 45	-6.0 <u>+</u> 3.83 -8.1+2.72	635 <u>+</u> 274 555 +187	21.9 <u>+</u> 5.09 24.2+4.55
5	65 <u>+</u> 39	-8.9 <u>+</u> 2.72	460 ± 88	25.8+4.22
6	50 <u>+</u> 30	-10.7 <u>+</u> 3.25	440 <u>+</u> 115	26.5 <u>+</u> 4.67

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Title: GENERAL ANESTHESIA FOR CESAREAN SECTION. SUPPLEMENTATION WITH EITHER ISOFLURANE OR HALOTHANE

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Introduction. The use of nitrous oxide-oxygen alone for maintenance of general anesthesia for Cesarian Section is associated with an unacceptable incidence of maternal awareness (1) which is reduced by the addition of low concentrations of the more potent inhalation agents (2). This study compares the effect of supplementation of 50% nitrous oxide-oxygen with either halothane or

equivalent concentration of the more recently introduced isoflurane for this operation.

Method. The protocol was approved by the Medical Ethical Research Committee and verbal consent from all patients was obtained. Healthy women for Cesarean Section were randomly allocated to receive either halothane or isoflurane. Following preoxygenation and institution of lateral tilt, anesthesia was induced with thiopental 4 mg kg⁻¹ followed by 100 mg succinylcholine and tracheal intubation. Maintenance anesthesia was with 50% N₂O in O₂ supplemented by either 0.5% halothane or 0.75% isoflurane until delivery, when N₂O was increased to 70%. The halothane or isoflurane was continued until the beginning of skin closure. Muscle relaxation was maintained by an 0.1% infusion of succinylcholine and alfentanil 1.0 mg was given i.v. immediately after delivery.

Patients were ventilated with a tidal volume of 10 ml kg⁻¹ at a rate of 12 breaths per minute with end tidal carbon dioxide, FlO₂ and inspired concentration of the inhalation agent being monitored. Oxytocin 5 units was given intravenously at delivery to promote uterine contraction with further increments given for persistent uterine relaxation or bleeding.

The EKG and arterial blood pressure were monitored throughout and maternal arterial and umbilical venous and arterial pH and blood gas tensions were measured at delivery. The Apgar scores of infants were recorded at 1 and 5 minutes from birth. The surgeon graded uterine tone on an unmarked 10 cm visual analogue scale (VAS) and this, together with the need for supplementary doses of oxytocin give a clinical indication of uterine relaxation. Recovery was timed from end of anesthesia until response to commands. All patients were questioned at 24 hours with regard to intraoperative dreams or awareness.

Where applicable findings are expressed as mean+SD. Significance levels were calculated by student 't' test.

Results. Twenty-five patients received isoflurane and 24 halothane. The two groups were comparable with regard to mean age, weight, period of gestation and preoperative hemoglobin and hematocrit values.

The uterine incision to delivery times for the isoflurane and halothane groups were 2.2±1.4 and 1.94±0.9 min respectively. Systolic blood pressure

fell below 100 mm Hg in 4 of the isoflurane series and in 2 given halothane. The average amount of infused succinylcholine was less in those given isoflurane, $(174\pm63 \text{ mg})$ as compared to halothane $(204\pm74 \text{ mg})$, but the difference was not statistically significant. Uterine relaxation was significantly greater in patients given halothane (P=0.03).

No patient in the investigation reported dreams or awareness during anesthesia. $\ensuremath{\mathbf{C}}$

The Apgar scores are similar in both series (Table 1). Blood gas analyses show no difference between the two series (Table 2). Recovery time was significantly shorter in the isoflurane series, 2.6 ± 1.4 min as compared to 4.4 ± 2.0 (P = 0.001) following halothane.

Table 1. Apgar scores (range) in the two series.

	1 min	5 min
Halothane		<u></u>
Mean	6.7	8.8
Range	(4-8)	(8-10)
Isoflurane		
Mean	7.4	8.9
Range	(5-8)	(7-9)

Table 2. Blood gas and pH data at delivery.

	Halothane	Isoflurane
рн		
Maternal	7.37+0.05	7.36+0.05
Umbilical vein	7.30+0.04	7.30+0.05
Umbilical artery	7.27+0.04	7.26+0.05
PCO ₂ KPa	_	_
Maternal	4.5 +0.88	4.2 +1.00
Umbilical vein	6.0 + 1.05	5.6 + 1.16
Umbilical artery	6.5 +1.43	6.1 +1.03
PO ₂ KPa	-	_
Maternal	21.9 +6.47	19.0 +8.90
Umbilical vein	4.9 ± 0.86	4.6 +1.36
Umbilical artery	3.2 ± 0.84	3.5 <u>+</u> 1.03

<u>Discussion</u>. Isoflurane in 0.75% concentration is a satisfactory supplement to nitrous oxide-oxygen mixture for general anesthesia in obstetrics and has the added advantage over halothane of a more rapid recovery.

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EFFECTS OF DIAZEPAM AND FLUMAZENIL ON SEDATION AND HYPOXIC VENTILATORY RESPONSE Title:

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Introduction. Diazepam is commonly used for sedation during diagnostic procedures. Studies designed to assess the effect of diazepam on respiratory function have yielded conflicting results. 1-5 The respiratory response to diazepan is affected by the dose and rate of administration. as well as by methodologic and individual factors (e.g., anxiety). While carbon dioxide (CO2 responsiveness may not be affected by sedative doses of diazepam, respiratory drive can be depressed. 1,3,4 Furthermore, investigators have reported a positive correlation between level of sedation and degree of ventilatory depression. 5,8 Although flumazenil (a specific benzodiazepine antagonist) effectively reverses the sedative effects of diazepam, 7 its ability to reverse diazepam-induced respiratory depression has not been evaluated. Therefore, we assessed the effect of flumazenil on the hypoxic ventilatory response to diazepam.

Methods. Seven healthy, consenting, unpremedicatec adults undergoing diagnostic procedures were studied according to a protocol approved by the Institutional Review Board. One hour prior to their scheduled procedure, patients underwent control evaluations of level of alertness/sedation and isocapnic hypoxic responsiveness. Alertness was assessed by a trained observer using a gradec scale (1=unresponsive to 5=fully alert). Sedation was evaluated by the patient using a 100 mm linear analog scale (0=awake/alert to 100=unresponsive/ asleep). Isocapnic hypoxic ventilatory responsiveness was assessed using a previously described rebreathing method. 8 This technique involves having subjects rebreathe from a 6-liter bag containing a gas mixture of 24% O2, 7% CO2 and balance N_2 . Oxygen in the circuit falls as O_2 is consumed and normocarbia (+1 torr) is maintained using a CO₂ absorber. Arterial O₂ saturation was measured using ear pulse oximetry. Hypoxic responsiveness was quantified by dividing the change in minute ventilation ($\Delta \tilde{V}_E$) by the change in arterial O_2 saturation ($\Delta L/\min/\$$ sat). (\tilde{V}_E) was determined on an 8 breath averaging basis at arterial O_2 saturations from 100% through 75%. Forty to seventy points were used to construct each hypoxic response curve according to the method of least square regression analysis. Intravenous diazepam, 2.5-5 mg boluses, was administered to maintain a stable level of sedation in which the patient was asleep but responsive to verbal commands. After the procedure, the state of consciousness and hypoxic ventilatory response were measured. These variables were then re-evaluated 5-10 min after flumazenil, 1.0 mg iv. Data were analyzed using unpaired t-tests and repeated measures of analysis of variance, with p<0.05 considered statistically significant. Data are reported as mean values +

Results. Demographic data and baseline values for sedation and hypoxic responses are summarized in table 1. Despite receiving an average diazepam dose of 1 mg/min, only four of the seven patients manifest depressed hypoxic responsiveness. Although the diazepam dosages (1.08 vs. 0.95

mg/min) and change in sedation scores (+85 vs. +81 mm) were comparable for the depressed and nondepressed subjects, the average duration of sedation differed significantly between the two groups (79 vs. 153 min). As expected, flumazenil rapidly and effectively reversed diazepam-induced sedation in all subjects (table 2). However, flumazenil reversed diazepam-induced respiratory depression in cnly one of the four subjects with decreased hypoxic responses. Ventilatory hypoxic responsiveness was unchanged after flumazenil in six of the seven patients studied. In addition, there was no correlation between level of consciousness and 02 responsiveness following flumazenil reversal.

Discussion. Analogous to the findings of Bailey et al., marked variability was noted in the ventilatory responses to diazepam. Since respiratory depression was not present following prolonged diazepam administration (>115 min), these data would suggest that tolerance may develop to the central respiratory effects of diazepam. In those patients manifesting depression of ventilatory drive, flumazenil did not reliably reverse diazepam-induced respiratory depression. In fact, the subject who displayed reversal of ventilatory depression was noted to be extremely anxious after flumazenil administration. Thus, these data would suggest that doses of flumazenil (0.5-1 mg iv) which effectively reverse benzodiazepine-induced sedation may not reverse residual respiratory depression. Further studies of the ventilatory effects of flumazenil in the presence of an opioidbenzodiazepine combination are clearly needed.

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Table	<u>l</u> : Age (yr)	Weight	Sedation score (mm)	Hypoxic response (L/min/%sat	Duration sedation (min)	Diazepam dosage (mg)
1 - M	39	77	54	4.0	55	55
2 - F	32	52	2	1.2	85	80
3 - F	42	60	3	2.5	85	115
4 - F	36	54	0	3.1	135	210
5 - F	44	95	7	3.2	115	110
6 - M	38	64	0	1.1	210	72
7 - M	36	82_	0	2.5	90	95
Avg.	38±4	69±16	9±20	2.5±1.1	111±51	105±51

Table 2:	Baseline values	Post- diazepam	Post- flumazenil
Alertness score	5.0	1.3±0.4*	5.0
Sedation score	9±19	93±19	26±26†
Hypoxic response			•
≤ 90 min (n=4)	2.5±1.1	1.4±0.8*	1.7±1.1
> 115 min (n=3)	2.5±1.2	2.6±0.9	2.7±0.8
*Significantly diff	erent from	baseline,	p<0.05
+Significantly diff			

ISOFLURANE IS DEFINITELY A LESS POTENT MYOCARDIAL DEPRESSANT THAN EITHER HALOTHANE OR Title:

ENFLURANE IN ISOLATED VENTRICULAR MYOCARDIUM.

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Introduction. In vivo studies suggested that isoflurane's (I) negative inotropic effects are less pronounced than those of either halothane (H) or enflurane (E) (1). This contrasts with reports that I and H caused equivalent myocardial depression in the cat papillary muscle (2). The purpose of this study was to critically evaluate inotropic effects of H, E, and I at equipotent anesthetic doses in isolated ventricular myocardium.

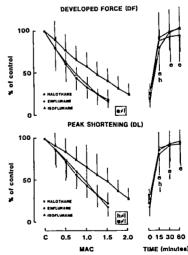
Methods. Twenty-seven papillary muscles of the right ventricle of adult male ferrets were mounted in a temperature controlled (30°C) chamber closed to the ambient atmosphere and that contained a physiological salt solution (mM): Na⁺ 135; K⁺ 5; Ca²⁺ 2.25; Mg²⁺ 1; Cl⁻ 103.5; HCO₃ 24; HPO²⁻ 1; SO²⁻ 1; acetate⁻¹ 20; glucose 10, continuously bubbled with 95% O₂-5% CO₂ (500 ml/min). Muscles were held between a force-length servo transducer (Innovi, Belgium) and a subminiature lucite clip with a built-in stimulation electrode (stimulus interval 4 seconds, 10% above threshold). After stabilization, a cumulative dose response curve for H (n=9), E (n=9), and I (n=9) was obtained for variables of contraction and relaxation. Anesthetic vapor was added to the gas mixture by means of an in-line vaporizer in increments of 0.25 MAC up to 1.50 MAC of H and E and up to 2.00 MAC of I. Anesthetic MAC values had been determined in ferrets previously. Vapor concentrations were set in the gas phase with a calibrated acoustic detector. Muscles contracted isotonically throughout with the initial muscle length set at L_{max} . At steady state after 15 minutes in each anesthetic concentration, we determined from an isometric, a preload isotonic, and a "zero-load-clamp", respectively: peak developed force (DF), maximal rate of rise (+dF/dt) and of fall of force (-dF/dt), peak isotonic shortening (DL), peak isotonic shortening and lengthening velocity (+V, -V), and maximal unloaded velocity of shortening (MÚVS). To test the hypothesis whether there was a dose response relationship for a particular contractile variable to a given anesthetic, and whether there were differences between anesthetics, relationships between contractile parameters and anesthetic dose were subjected to response curve analysis by least square linear regression whenever possible. Data are mean ± SD.

Results. H, E, and I caused a dose-dependent reversible decrease of all variables of contraction (DF, +dF/dt, DL, MLVS) and of relaxation (-dF/dt, -V). For these variables the relationship between dose and effect was linear. For variables of isometric muscle performance, differences between anesthetics were confined to differences between I and E. For variables of isotonic muscle performance, I was different from both H and E. At no time did we detect any statistically significant differences of effect between H and E.

<u>Discussion</u>. The negative inotropic effects of I are clearly less than those of either H or E at

equipotent anesthetic doses in mammalian ventricular myocardium. There was previously no agreement on the relative potencies of the three anesthetics regarding their myocardial depressant effect among in vitro studies (2,3,4). Although the negative inotropic effect of halogenated inhalational anesthetics is a very well known property of these drugs, this is the first study on ventricular cardiac muscle in which these three halogenated anesthetics have been compared in absolutely identical conditions of temperature, experimental protocol and muscle characteristics, and equipotency of anesthetic concentration. In this study E was significantly more depressant than I for both isometric and isotonic parameters. H and I differed for isotonic parameters only, but not for the isometric ones. This can be partly explained by a greater coefficient of variation in the isometric parameters. However, parameters of isotonic muscle performance reflect more closely the physiological mode of contraction of cardiac muscle in the intact heart, and may be more sensitive indicators of drug action that are isometric parameters. In conclusion it would appear that intrinsic depressant effects that are less pronounced for I account for substantial fraction of its more benign hemodynamic effects in vivo in comparison with H and E.

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e, h, i: p < 0.05 versus control (C)

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LOWERED PERFUSION FLOW RATES DURING HYPOTHERMIC CERDIOPULMONARY BYPASS DO NOT IMPAIR CEREBRAL OXYGENATION
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INTRODUCTION

When alpha-stat acid-base management is employed, cerebral blood flow (CBF) has been demonstrated to autoregulate over a wide range of perfusion pressures. The CBF has similarly been shown to be adequately maintained during hypothermic cardiopulmonary bypass (CPB) when flow rates are transiently lowered into the range of 1.0 - 1.25 l.m - min - 1.73 The effects of maintaining lowered perfusion for the duration of hypothermic CPB on CBF, cerebral metabolic rate for oxygen (CMRO₂), systemic oxygen consumption index (VO₂I) and arterial lactate concentration has not previously been reported in man.

METHODS

Following institutional approval and after obtaining written informed consent, 5 patients undergoing elective cardiac surgery were anesthetised with sufentanil 5 - 12 mcg.kg and 100% O₂. Immediately prior to institution of CPB patients received 0.15 mg.kg pancuronium. Nonpulsatile perfusion using a membrane oxygenator and arterial line filtration was maintained for the duration of hypothermic CPB (26-28) C) at perfusion flow rates of 1.0 - 1.25 1.m min During normothermic CPB pump flow was 2.0 - 2.4 1.m min T. Temperature uncorrected PaCO was maintained at approximately 40 mmHg (alpha-stat).

CBF was measured using 5-6 mCi of $^{133}\mathrm{Xe}$ in 6 ml saline injected into the arterial port of the pump oxygenator. Mean CBF was determined from the average 133 Xe clearance measured by 5 scintillation detectors located over the right cerebral hemisphere. Standard correction factors were used to compensate for changes in xenon partition coefficient due to temperature and hematocrit. A 15 cm 16 ga catheter was threaded retrograde into the right internal jugular bulb for sampling effluent cerebral venous blood. Cerebral perfusion pressure (CPP) was calculated as the difference between mean arterial (MAP) and jugular venous pressures. Blood gas measurements were made using a Radiometer ABL2 and oxygen saturation was measured directly using a Radiometer OSM3 hemoximeter. CMRO, was calculated as the product of the O₂ content difference between arterial and jugular venous blood and mean hemispheric CBF. VO₂I was calculated as the product of the perfusion flow rate indexed to body surface area (QI) and the O2 content difference between arterial and mixed venous blood. Nasopharyngeal temperature (NPT) was

taken as cerebral temperature while rectal temperature (RT) was used as systemic temperature. Two measurements at least 30 min apart were made during hypothermic CPB once a stable NPT had been reached. One further CBF determination was made during normothermic CPB when NPT had reached $37^{\circ}\mathrm{C}$.

Multiple stepwise linear regression analysis with CMRO₂ vs. CBF, CaO₂, CPP, QI, and NPT was used to assess factors influencing cerebral and systemic oxygen consumption respectively. An alpha of 0.05 and beta of 0.8 were used as measures of significance.

RESULTS

Fourteen suitable CBF and CMRO₂ studies were obtained in 5 patients. One study was omitted due to insufficient time. There were no significant differences in CBF (17.1 \pm 3.1 ml.100g $^{-1}$, min $^{-1}$) or CMRO₂ (0.51 \pm 0.09 ml.100g $^{-1}$.min $^{-1}$) at either time during hypothermic (NPT = 27.2 \pm 1.1 °C) CPB. CMRO₂ varied significantly only with NPT (p<0.0001) where CMRO₂₂= -1.35 + 4.06 NPT. Mean QI was 1.25 \pm 0.12 1.m $^{-1}$.min $^{-1}$. VO.I averaged 35.5 \pm 5.3 ml.m $^{-2}$.min $^{-1}$ at a mean RT of 30.1 \pm 1.0 °C. There was no significant change in arterial lactate concentration during hypothermic CPB.

DISCUSSION

The values for CBF and CMRO, reported here are similar to those observed during hypothermic CPB using perfusion flow rates of 2.0 - 2.5 l.m².min¹. These results demonstrate preservation of cerebral oxygen consumption with perfusion flow rates maintained at 1.25 l.m².min¹ during hypothermic CPB. Lowered perfusion flow rates have the potential to reduce trauma to blood elements and reduce rewarming of the myocardium without jeopardizing cerebral oxygenation.

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Title: PACKED RED CELLS FOR BLOOD REPLACEMENT: WHEN IS FFP REQUIRED?

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The increased use of packed Introduction. red cell concentrates instead of units of whole blood to replace major blood loss is believed to be one of many factors responsible for a 10-fold increase in fresh frozen plasma (FFP) use over the last decade. Because the indications and Because the indications benefits of fresh frozen plasma administration in 1,2,3 situations of major blood loss are unclear, the purpose of this study was to document the changes coagulation that occur packed red cell and crystalloid solutions are used to replace major blood loss, and to determine when FFP might be indicated.

Methods. After consent was obtained from the institution's human studies committee, 12 patients who required major elective surgery were studied. None of the patients had a history or physical examination suggestive of a bleeding disorder. At the start of the operative procedure, an initial clotting profile which included prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, FDP, thrombin time, platelet count and factor assays of V, VIII, and IX were obtained along with an hematocrit and arterial blood gas. After approximately every one-third blood volume was replaced, repeat measurements of the coagulation profile, hematocrit and arterial blood gases were performed. Packed red cell concentrates and crystalloid solutions were used for blood replacement.

The quality of clot formation and the degree of bleeding that occurred from wound edges was assessed clinically and with the results of coagulation tests used as an indication for platelets and if necessary FFP.

Results. Decreases in platelet count occurred as greater fractions of blood volume were replaced. Factor I and Factor V (Figure 1) decreased as the original blood volume was diluted with packed red cells and crystalloid. Despite the presence of a prolonged PT and aPTT in 9 of the 12 patients, none of the patients manifested increased bleeding tendency with blood replacement up to and including one blood volume (Figures 2 and 3). In four patients, when excessive clinical bleeding was noted, platelet concentrates were administered (platelet count < 75,000). In two patients this improved, but did not resolve the observed poor clot formation and FFP was required. In these two patients, the PT and PTT was greater than twice control prior to FFP and Factor V levels were less than 30%. In two patients who were replaced with 1.8 and 2.0 blood volumes respectively neither platelets nor FFP were indicated during the study. No bleeding complications occurred in the postoperative period.

<u>Discussion</u>. If an elevation of PT and aPTT were the only criteria for the use of FFP, then 9 of 12 patients would have required FFP prior to one blood volume replacement. FFP did reverse inadequate clinical hemostasis in two patients who required greater than one blood volume replacement and despite correction of thrombocytopenia had

increased clinical bleeding. When packed red cell concentrates are used to replace major blood loss, FFP may be required. The indications for coagulation factors can be determined by clinical assessment of hemostasis and monitoring the coagulation profile.

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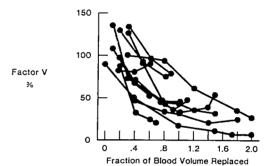
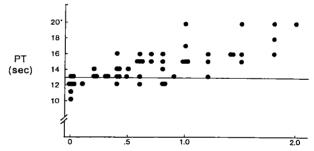
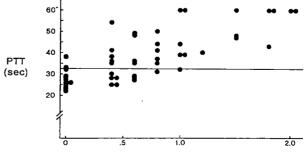


Fig. 1: Factor V levels with increasing blood volume replacement. Each patient is represented by a solid line.



Blood Volumes Replaced

Fig. 2: Scattergram of Prothrombin Times (PT) in sec with increasing blood replacement. (solid line @ 13 sec - upper limit of normal PT)



Blood Volumes Replaced

Fig. 3: Scattergram of Partial Thromboplastin Time (PTT) in sec with increasing blood replacement (solid line @ 33 sec - upper limit of normal PTT)

Title: CARDIOVASCULAR EFFECTS OF HALOTHANE AND ISOFLURANE IN INFANTS: THE EFFECT OF NITROUS OXIDE

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Introduction. In adults, less cardiovascular effects occur when NoO is used to supplement halothane or isoflurane anesthesia than when equianesthetic concentrations of halothane and isoflurane alone are used. 1,2 The comparative cardiovascular effects of equianesthetic levels of halothane and isoflurane with and without NoO have not been measured in infants. This study used pulsed doppler echocardiography to compare cardiovascular changes that occur in infants during equianesthetic levels of halothane or isoflurane anesthesia with and without NoO.

Methods. After informed written parental consent was obtained, we studied 28 ASA I infants, who required elective surgery. Ten to thirty minutes prior to induction of anesthesia, these unpremedicated infants had cardiovascular parameters recorded using pulsed doppler and two dimension echocardiography. The non-invasive cardiovascular data collected included blood pressure and heart rate, two dimension echocardiographic measures of left ventricular area and length, and pulsed doppler echocardiography measures of mean pulmonary artery velocity.

Anesthesia was induced by mask via semiclosed circuit with 3 1 N_2 0 and 2 1 0 with halothane (n = 14) or isoflurane (n = 14). Ventilation was controlled with end-tidal gas measurements monitored using a Perkin-Elmer mass spectrometer. With the end-tidal anesthesia concentration maintained for five minutes at 60% No and 0.9 MAC (adjusted for age) halothane or isoflurane (approximately twenty minutes following induction of anesthesia), the cardiovascular measurements were repeated. The nitrous oxide was discontinued and the inspired anesthetic concentration increased to achieve a 1.5 MAC endtidal level of either halothane or isoflurane. After the 1.5 MAC end-tidal concentration had been maintained for five minutes, a third set of cardiovascular data was collected. All data was collected prior to intubation and the start of elective surgery.

The results are expressed as mean \pm SEM and were analyzed by two way ANOVA.

Results. The ratio of end-tidal to inspired levels of halothane or isoflurane (F_{et}/F_i) was 0.83 \pm 0.04 at the time the cardiovascular data was collected during anesthesia.

Heart rate (HR) and mean blood pressure (MBP) decreased from awake values at 1.5 MAC (60% nitrous oxide and 0.9 MAC halothane or isoflurane) and at 1.5 MAC halothane and isoflurane alone.

Cardiac output decreased from awake, similar and significant amount with both halothane and isoflurane in combination with nitrous oxide and with halothane and isoflurane alone at 1.5 MAC end-tidal levels (Fig. 1).

With No0 in combination with halothane and halothane afone at 1.5 MAC, ejection fractions decreased 24% and 22% respectively from control levels. In the infants who received isoflurane, ejection fraction decreased 18% and 16% from

control with 1.5 MAC No0 and isoflurane and 1.5 MAC isoflurane respectively (Fig. 2).

The addition of NoO to either Discussion. halothane and isoflurane in infants when compared to either agent alone at 1.5 MAC produced similar cardiovascular effects as manifested by MBP, cardiac output and ejection fraction. In adults, No produces direct myocardial depression and stimulation of the sympathetic nervous system which may be the reason that less cardiovascular effects are observed when N₂0 is added to halothane or isoflurane than with either agent alone.3 Perhaps the autonomic and cardiac responses to NoO are different in infants and for this reason, similar cardiovascular effects occur at equianesthetic levels of halothane or isoflurane with and without N20.

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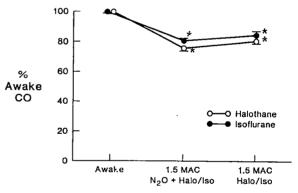


Fig. 1: Percent of awake cardiac output (C.O.) with 1.5 MAC No0 and halo/iso and Results are expressed halo/iso alone. as mean + SEM. p < 0.05 from awake.

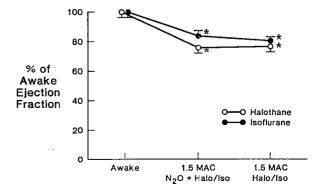


Fig. 2: Percent of awake ejection fraction (EF) with 1.5 MAC N₂0 and halo/iso and halo/iso alone. Results are expressed as mean – SEM. $\hat{p} < 0.05 \text{ from awake.}$

Title:

SPINAL MECHANISM OF CLONIDINE ANALGESIA AND ITS SYNERGISM WITH MORPHINE

Authors: Affiliation:

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Introduction. Clonidine, alpha-2 adrenergic agonist, applied spinally or epidurally has been shown to be effective in blocking noxious stimuli in animal studies (1) and in human applications (2). The purpose of this inestigation is to evaluate the mechanisms of spinally administered clonidine to produce analgesia, utilizing a sensitive neurophysiologic assay method, and to evaluate combined effects of clonidine and morphine.

Methods. Cats were initially anesthetized with halothane, nitrous oxide and oxygen for surgical procedures, which included a tracheostomy, arterial and venous cannulation, lumbar laminectomy, and mid-collicular decerebration. A minimum of two hours separated the spinal cord transection and beginning of neuronal recording. Neuronal activity was recorded from wide dynamic range (WDR) neurons of the dorsal horn. Noxiously evoked activity was produced by the presentation of a 51°C radiant heat stimulus for 8 seconds applied on the neuron's receptive field. Following control studies, drugs in saline (0.5ml, 37°C) were applied onto the spinal cord. The drugs applied were clonidine, 5ug (n = 8), 10ug (n = 8), 30ug (n = 14), and morphine, 25ug (n = 8). After the drug application, neural activity was monitored every 3 minutes for a minimum of 30 minutes.

Results. Data was obtained from forty-six animals. The 5ug of clonidine applied over the spinal cord produced no suppression of WDR neuron activity. The loug of clonidine produced a mild suppression (35% at 30 mins), the 30ug of clonidine produced a significant suppression (61% at 30 mins.) of the noxiously activity. The suppression of noxiously evoked activity was reversed by the systemic administration of yohimbine. In spite of the fact that 5ug of clonidine and 25ug of morphine alone did not produce any discernible suppression of WDR neurons for 30 minutes, the combined clonidine 5ug and morphine 25ug yielded significant suppression (approximately 50% at 30 mins.) of mean evoked activity.

Discussion. Neuropharmacological studies on pain transmission suggest that the spinal cord is

an important site of action. The suppression of spinal neurons by clonidine, reversed by yohimbine, selective alpha-2 antagonist, supports the results of previous reports indicating that the analgesic efficacy of clonidine is a result of its alpha-2 agonistic activity acting on the spinal nociceptive neurons. The combination of low dose morphine and clonidine, resulting in a synergism, is an important finding and would be a useful tool for spinal analgesia by avoiding or lessening the side effects of both agents.

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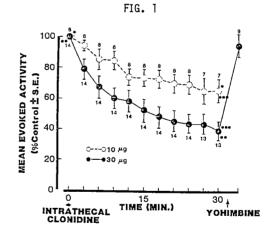


Fig. 1. Effects of clonidine loug and 30ug on the mean evoked activity of wide dynamic range (WDR) neurons. The suppression by 30ug of clonidine was reversed by yohimbine 0.5 to 1.5mg/kg i.v.

(Supported by NIH Grant NS-09871)

Title: LOCAL ANESTHETIC TOXICITY ON VASCULAR MUSCLE CONTRACTILITY: 1. MYOSIN AND

CALMODULIN-DEPENDENT MYOSIN LIGHT CHAIR KINASE

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INTRODUCTION: Although the depressant effects of anesthetics on the hemodynamics and contractility of cardiac and vascular smooth muscle have been well recognized, reports on the biochemical effects, especially at the contractile protein level, are few. Contrary to the skeletal muscle, smooth muscle contraction is initiated by phosphorylation of the myosin followed by the interaction between the phosphorylated myosin (active myosin) and the actin. The phosphorylation of the smooth muscle myosin from ATP occurs in the light chain (molecular weight 20,000) by the action of the myosin light chain kinase (MLCK) in the presence of calmodulin and calcium ion. We postulate that the hemodynamic depression by anesthetics involves the smooth muscle contractile protein system. This study concerns the phosphorylation of the myosin light chain catalyzed by the MLCK.

METHOD: The smooth muscle myosin and the myosin light chain kinase were prepared from the fresh turkey gizzard by the method described by Dabrowska et al¹ and Adelstein et al, respectively. The extracted myosin was free from myosin light chain kinase activity and was the inactive form (non-phosphorylated light chain). Calmodulin was obtained from Bio-Rad. The assay consisted of determining the degree of phosphorylation of the smooth muscle myosin by the MLCK in the presence of ATP, calcium ion, and calmodulin. The total assay mixture consisted of 1 mM ATP, 1°10 M CaCl, 5 mM MgCl, 80 mM KCl, and 20 mM Trismalate buffer pH 6.8 in total volume of 100 ul. The reaction was started by the addition of ATP at C and stopped after 5 min by the addition of 8 M urea. The myosin phosphorylation was determined by the urea-polyacrylamide gel electrophoresis as described by Chacko et al. The phosphorylated light chain moves faster than the nonphosphorylated light chain in the gel electrophoresis. Clinical concentrations of volatile anesthetics were added to the reaction mixture by diffusion from the gas phase delivered by anesthetic specific vaporizers. The anesthetic concentrations were confirmed by a Shimadzu gas chromatograph. Local anesthetics were added as hydrochloric acid salts. The pH of the reaction mixture was letermined after the addition, and the pH was readjusted when required.

RESULTS: The inhibition by local anesthetics was in the order of tetracaine > bupivacaine > lidocaine. Lidocaine was almost without effect intil the concentration exceeded 1°10 M, whereas tetracaine inhibited the MLCK more than 50% at 5°10-3 M. Halothane and isoflurane showed weak depressant effect at 1.5%. These inhibitory effects of local anesthetics were not reversed by raising the calcium ion concentration to 1°10 M. In contrast, an increase in the calmodulin concentration from 1°10 to 1°10 M antagonized the anesthetic depression from the local mesthetics as well as the volatile anesthetics.

DISCUSSION: It is generally believed that the inhibitory action of local anesthetics upon a variety of calmodulin-dependent enzymes (membranebound guanylate cyclase, cyclic nucleotide phosphodiesterase, etc.) is caused by the interaction with calmodulin. There are some published data on the local anesthetic inhibition of these enzymes being antagonized by an increase in the calmodulin concentration but not by calcium ion. The present results with local and volatile anesthetics support these findings. It has been postulated that the association of calcium ion with calmodulin initiates conformational change of calmodulin and exposes hydrophobic domain in the calmodulin molecule to the surface. The calcium-induced exposure of hydrophobic domain of calmodulin appears to be the main mechanism for the activation of calcium-calmodulin-dependent systems. It is possible that anesthetic molecules interact with the hydrophobic domain and control the calmodulin activity. The relatively benign effect of lidocaine on the hemodynamics may be related to its weak action on the smooth muscle contractile mechanisms. The turkey gizzard smooth muscle is generally considered to represent the properties of vascular smooth muscle. Local anesthetic toxicity may be comprised of a cardiac and a vascular component. Local anesthetic toxicity is manifested by hemodynamic depression and often electrical activity of the heart continued after total cardiovascular collapse. These observations suggest a subcellular mechanism for the vasodilating effects of local and inhalational anesthetics.

ACKNOWLEDGEMENT: Supported in part by the Veterans Administration Research Service and NIH Grants GM26950 and GM27670.

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Title: WASHIN AND WASHOUT OF ISOFLURANE DURING CARDIOPULMONARY BYPASS

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Introduction. Although volatile anesthetic agents are frequently added to the gas given through the oxygenator during cardiopulmonary bypass (CPB), anesthetic washin and washout by this route have not been studied in patients. We measured the partial pressure of isoflurane in arterial (Part) and venous (Pven) blood, and in the gas exhausted from the oxygenator (Pex), during hypothermic CPB. Three questions were addressed: 1) How rapidly does Part rise during washin and decline during washout?

2) What is the uptake and elimination of anesthetic, as reflected by the arterial-to-venous partial pressure difference? 3) Does Pex reliably reflect Part? If so, measurement of Pex, e.g., by mass spectrometry, would allow close approximation of Part during CPB.

Methods. Following approval of the Committee on Human Research, seven patients undergoing cardiac operations were studied. Prior to CPB, isoflurane was not administered. CPB circuits were assembled as usual, including Bentley-10B (n = 4) or Shiley-S-100A (n = 3) bubble oxygenators primed with 2000 ml of lactated Ringer's solution. The mean Hgb concentration during CPB was 7.2 ± 0.9 mg/dl. After establishing hypothermic CPB at a stable temperature (mean temperature = $24.6 \pm$ 2.5 °C), isoflurane 1% was added to the oxygenator gas inflow. Immediately before the addition of isoflurane, and at 1, 2, 4, 8, 16, 32, and 48 min during addition of isoflurane, simultaneous gas and blood samples were obtained from the following locations: a) inlet gas tubing; b) exhaust gas outlet; c) arterial line tubing of the CPB circuit (arterialized blood); and d) venous return port (venous blood). Samples were also obtained immediately prior to rewarming. Isoflurane administration was discontinued as rewarming began, and samples were obtained at 1, 2, 4, 8, 16, and 32 min during washout. The study ended when controlled ventilation via the normal pulmonary route recommenced. During washin, mean gas flow rate was 3.5 ± 0.8 1/min and mean pump flow rate was 3.9 ± 0.4 1/min. During washout, mean gas flow rate was 4.1 ± 0.9 l/min, mean pump flow rate was 4.0 \pm 0.3 1/min, and mean temperature was 34.5 \pm 0.8.

The concentration of isoflurane in all samples was determined by gas chromatography. Concentrations were converted to partial pressures, using the blood/gas partition coefficient (1.35 ± 0.19) as determined in each study (corrected for the instantaneously-measured temperature of each sample). Analysis of linear regression was used to determine the relationship between P_{axt} and P_{ex} .

Results. P_{ex} , P_{axt} , and P_{ven} progressively rose toward inlet gas partial pressure (P_{ins}) during washin (Figure 1). After 48 min of washin, P_{art} was 55%, and P_{ven} 37%, equilibrated with P_{ins} . P_{ven} , P_{axt} , and P_{ex} [each expressed as a ratio of the peak arterial partial pressure (P_{axt}) obtained just before cessation of isoflurane administration] rapidly declined during washout (Figure 2). After 32 min of washout, P_{art} had declined to 13% of its peak, while P_{ven} had declined to 23% of P_{art} . P_{ex} overestimated P_{art} during washin [slope = 0.74 \pm 0.07, standard error of the estimate (SEE) = 0.07, r^2 = 0.70] and underestimated P_{art} during washout [slope = 0.80 \pm 0.06, SEE = 0.05, r^2 = 0.80].

Discussion. Washin of isoflurane occurred somewhat more slowly during CPB than during administration via the normal pulmonary route in normothermic patients. However, during the rewarming phase of CPB, washout occurred as rapidly as from the lungs of normothermic patients. The slower rise in Part during CPB may be explained by the greater tissue capacity produced by hypothermia and a blood/gas partition coefficient equal to that found in normothermic non-hemodiluted patients. The normal decay rate during washout may be the result of a declining blood/gas partition coefficient (due to rewarming) and the counterbalancing existence of relatively high tissue stores of anesthetic. Our data support the suggestion made by Waller et al.(1) that 15 min of washout is sufficient to eliminate the major fraction (75%) of volatile anesthetic from arterial blood during CPB. Therefore, the potential for residual myocardial depression should be minimized after 15 min. Finally, although Per did not precisely reflect Part, its proximity was sufficient to make it a useful estimate.

FIGURE 1: ISOFLURANE WASHIN DURING CPB

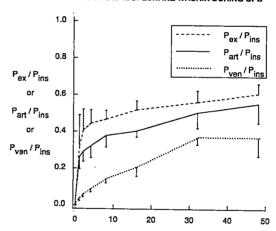
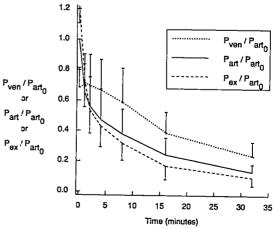


FIGURE 2: ISOFLURANE WASHOUT DURING CPB



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TITLE:

HIGH DOSE SUFENTANIL DOES NOT FREVENT CATECHOLAMINE RESPONSES TO HYPOTHERMIC CARDIOPULMONARY BYPASS

AUTHORS:

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Introduction: The use of high dose narcotic base anesthesia with fentanyl is a widely accepted technique primarily because of the minimal hemodynamic effects. Attempts to prevent or blunt the catecholamine responses to stress, particularly during cardiopulmonary bypass(CPB), have been less successful even with very high doses. This study was undertaken to determine if high doses of sufentanil, seven to ten times as potent as fentanyl, could prevent the catacholamine response to CPB.

Methods: Ten patients scheduled for elective coronary artery surgery gave written informed consent and were studied with approval from the institutional review board. Patients were randomly assigned to receive either a 20 mcg/kg loading dose of sufentanil, and an infusion at 0.1 mcg/kg/min; or a 40 mcg/kc loading dose with an infusion of 0.2 mcg/kg/min. Infusions were discontinued at the beginning of CPB. Muscle relaxation was achieved with a combination of metocurine and pancuronium. During CPB, all patients were cooled to 25°C. Blood samples were obtained at seven points: 1) immediately prior to CPB; 2-4) every 15 minutes during CPB for 45 minutes; 5) during rewarming at 35°C (pharyngeal) immediately after separation from CPB and 7) 15 minutes after CPB. Plasma was separated by centrifugation and stored at -70°C until analyzed. Sufentanil levels were measured by radioimmunoassay. Epinephrine and norepinephrine were measured by radioenzymatic assay (REA) or high performance liquid chromatography (HPLC).

Results: Mean (+ SEM) plasma levels of epinephrine, norepinephrine and sufentanil at each time point are presented in Table Sufentanil levels were consistently higher in patients who received the higher dose of narcotic. In both groups, the level of sufentanil fell during CPB, and rebounded slightly upon discontinuation of CPB. Levels of epinephrine and norepinephrine were unrelated to the levels of sufentanil. There was a tendancy toward lower levels of catecholamines, and less variability in the high dose group. Plasma catecholamine levels rose during cardiopulmonary bypass in both groups. The only significant difference in catecholamines between the

groups was the higher level of epinephrine 15 minutes after initiation of CPB in patients who received the lower dose of sufentanil. In both groups, plasma epinephrine was elevated at the end of CPB relative to pre-CPB levels.

Table 1

<u>Time</u>	Dose (mcg/kg)	Epi (pg/ml)	Norepi (pg/ml)	Sufentanil (ng/ml)
D	40	205104		
Pre	40	105 <u>+</u> 24	427 <u>+</u> 104	10.33 <u>+</u> 0.5
CPB	20	141 <u>+</u> 23	464 <u>+</u> 68	7.07 <u>+</u> 0.3**
15"	40	149 <u>+</u> 16	371+62	4.59 <u>+</u> 0.4
CPB	20	248 <u>+</u> 25**	528 <u>+</u> 94	3.45 <u>+</u> 0.3*
30"	40	208 <u>+</u> 86	389+74	4.22±0.3
CPB	20	340 <u>+</u> 109	911 <u>+</u> 470	3.28 <u>+</u> 0.3*
45"	40	185+53	E664120	4 21 10 2
		_	566 <u>+</u> 120	4.31 <u>+</u> 0.3
CPB	20	279 <u>+</u> 104	880 <u>+</u> 325	3.32 <u>+</u> 0.3*
Warm	40	267+68 ^X	632+192	4.97 <u>+</u> 0.3
CPB	20	279 <u>+</u> 79 ^X	798 <u>+</u> 224	3.68 <u>+</u> 0.4**
Post	40	265+126	497+153	6.10 <u>+</u> 0.4
CPB	20	159 <u>+</u> 32	471 <u>+</u> 155	4.42 <u>+</u> 0.4**
250	40	104100	5661368	- 40.0 -
15"	40	124 <u>+</u> 20	566 <u>+</u> 168	5.49 <u>+</u> 0.5
	20	141 <u>+</u> 21	424 <u>+</u> 51	3.91 <u>+</u> 0.3**

*p<0.05; **p<0.01 between groups, xp<0.5, +p<0.01 vs. pre-CPB.

Discussion: Despite the very high blood levels, sufentanil did not prevent the humoral catecholamine response to the stress of hypothermic CPB. In contrast to the prebypass period, when sufentanilinduced anesthesia is associated with remarkably stable hemodynamic parameters and catecholamine levels during surgical stress, the period of CPB was accompanied by highly variable and rising catecholamine levels in spite of stable levels of sufentanil. Catecholamine responses during CPB are probably not related to adequacy of anesthesia, but more likely reflect humoral responses to other variables, such as hemodynamic changes, hemodilution or hypothermia which are not alleviated by anesthetic doses of synthetic narcotic analgesics. appears that elimination of the catecholamine response to CPB will not be achieved by administration of narcotics, even if more potent agents become available for clinical use.

TITLE:

MAINTENANCE DOSE VECURONIUM ON METOCURINE THE EFFECT OF INDUCED

NEUROMUSCULAR BLOCKADE

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INTRODUCTION. Significant progress has been made towards the goal proposed by Saverese and Kitz 1 for the development of short, intermediate and long duration competitive relaxants for surgical procedures of differing The situation arises not infrequently however, when the long acting relaxant administered at the start of the anesthetic provides inadequate relaxation for some crucial period near the end of the surgical procedure. A supplemental dose of the original relaxant given at this time may be ineffective, if the dose is small; or may prevent adequate reversal at the end of surgery, if the dose is large. Aps and Inglish have suggested that small doses of the intermediate duration muscle relaxants (atracurium and vecuronium) can be used to enhance and somewhat prolong the duration of neuromuscular blockade in the presence of residual pancuronium activity, without adversly affecting the reversability of paralysis at the end of the surgical procedure. In order to quantitatively evaluate the synergistic potential of this therapeutic regimen, this study was designed to compare the effect of a maintenance dose of vecuronium given during recovery from an intial dose of either metocurine or vecuronium. METHODS. A total of 16 consenting neurosurgical patients were studied with the approval of the Institutional Review Board. Patients with significant cardiovascular, renal, hepatic or neuromuscular disease, as well as those receiving medications known to affect neuromuscular blockade were excluded from the study. Based on the anticipated duration of the surgical procedure, patients were assigned to receive either metocurine 0.3 mg/kg or vecuronium 0.1 mg/kg during anesthetic induction. Preoperative medication was left to the discretion of the anesthesiologist assigned to each patient. All patients were induced with thiopental 4-8 mg/kg and isoflurane 2% inspired in oxygen. The ulnar nerve was stimulated at the wrist with 0.2ms duration supramaximal square waves at 0.1 Hz from a Grass S-44 stimulator in conjunction with a SIU-4678 stimulus isolation unit. When the neuromuscular response of the thumb adductors as measured by an FT-10 force-displacement transducer became stable, the bolus of muscle relaxant was intravenously selected intubation, the isoflurane administered. After concentration was reduced to 0.75% inspired in N2O and O₂ (2:1). When the monitored twitch response recovered to 25% of baseline control, a maintenance dose of vecuronium 0.015 mg/kg was given. The maximum response after this second dose of relaxant and the times required for 5 and 25% recovery of baseline twitch height were recorded. In the event that the second dose of relaxant did not provide 95% paralysis, the time required for the commencement of recovery from the second dose was used instead of the 5% recovery time. Temperature was maintained above 35°C with the aid of heating blankets. All patients were moderately hyperventilated to an EtCO₂ between 24 and 30 mmHg. Comparisons between groups were made with Student's two tailed t-test for unpaired data. The threshold for significance was

RESULTS. The results of this study are summarized in the TABLE. There were no significant differences between

p < 0.05.

groups in age or weight. The response to maintenance doses of vecuronium is markedly enhanced in both magnitude and duration in patients initially paralyzed with metocurine compared to those initially paralyzed with vecuronium

The sequential use of long acting DISCUSSION. neuromuscular relaxants followed by a relaxant of intermediate duration has previously been studied in an effort to optimize the "priming principal". The observed synergism is beneficial in providing satisfactory intubating conditions within an accelerated time period. The present study demonstrates similar synergism at the end of the surgical procedure, whereby the use of a small dose of vecuronium 0.15mg/kg during the recovery phase from a preexisting metocurine block led to profound blockade of prolonged duration. This same vecuronium dose following preexisting vecuronium blockade provides additional surgical relaxation (time to 25% recovery) lasting 17 ± 6 minutes, a reasonable time period for procedures such as peritoneal closure, while permitting predictable reversal (time to 5% recovery) within 9 [±] 4 minutes. With preexisting metocurine block however, the maintenance dose of vecuronium led to an approximately fivefold increase in the duration of surgical relaxation. importantly, it is felt that this block is not readily reversable for close to one hour. In this study, both groups of patients received the same maintenance dose of vecuronium, as a basis for comparison. It is likely that a smaller dose of vecuronium in the metocurine group could provide sufficient relaxation of a more appropriate duration. Formal dose-response studies along these lines are now being performed. Although less synergism may have occured with a combination of pancuronium and vecuronium, the agents chosen for this study were selected on the basis of their lack of cardiovascular side effects. REFERENCES. 1. Saverese JJ, Kitz RJ; Anesthesiology 42:236-239, 1975

 Aps C, Inglis MS; Anaesthesia 39:187, 1984
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TABLE. Magnitude and duration of response to vecuronium 0.015 mg/kg following 25% recovery from metocurine 0.3 mg/kg or vecuronium 0.1 mg/kg. MEAN (S.D.). n = 8 in

each group.			
eden groop.	VECURONIUM	METOCURINE	P<
AGE (yr.)	40 (7)	44 (1 <i>9</i>)	NS
WEIGHT (kg)	65 (11)	73 (15)	NS
MAX.RESPONSE (%)	92 (8)	100 (0)	0.02
5% RECOVERY (min)	9 (4)	53 (10)	0.001
25% RECOVERY (min)	17 (6)	81 (12)	0.001

TITLE: PHARMACOKINETICS OF EPIDURAL MORPHINE IN OBSTETRICAL PATIENTS

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Introduction. Epidural morphine (Duramorph) is popular for prolonged postoperative analgesia in obstetrical patients. Little information is available on plasma pharmacokinetics and urinary elimination of Duramorph in obstetrical patients. This study reports plasma and urinary levels of unconjugated (free) and total (conjugated unconjugated) morphine levels in postpartun patients.

<u>Methods.</u> The protocol was approved by the Review Board and patients (n=8) gave informed consent. Ringers lactate 1200 nI was used for prehydration prior to lumbar epidural anesthesia induced to T4 level with 2% lidocaine with 1:200,000 epinephrine for cesarean section. Duramorph 5 mg was injected through the epidural catheter after delivery. No other medications except pitocin was used. Venous blood (EDTŁ anticoagulant) and urine samples were collected prior to Duramorph (baseline) amd at 0.25,0.5,1, 2, 4, 8, 12 and 24 hours. Free morphine concentration was assayed using a specific radioimmunoassay (0.3% cross-reactivity with morphine-3glucuronide, Coat-A- Count, Diagnostics Products Corp, Los Angeles, CA). The concentrations of conjugated morphine is plasma and urine samples were measured following incubation at 37 deg C for 24 hours with glusulase (1) (Endo Labs, Garden City, N.Y; 4000 u beta glucuronidase + 70 u u sulfatase). A computer program was used produce logit-log transformation of the data following which a model-dependent pharmacokinetic parameters were generated. Area under the curve for each patient for the 0-24 hours period were calculated by the trapezoidal rule and polyexponential curve-fitting. The terminal half-life (t1/2-beta) was calculated by the regression analysis.

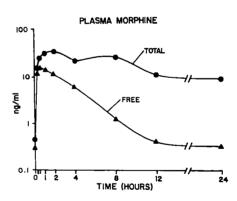
Results. Plasma: The free morphine peaked at 0.5 hour and the total morphine at 2 hours (Fig 1). Except at 0.25 and 0.5 hour the morphine glucuronide exceeded free morphine concentration. The total morphine peaked at 2 hours (Fig 1). Volume of distribution (VDss) and t-1/2-beta and clearance (Cl) are listed in Table. Total morphine showed decreased VDss and C. Urine: In the first two hours postglusalate measurements were not significantly different from free morphine (Fig 2). Significant amount of free morphine continued to be excreted even at 24 hours, a value 30 times greater than the corresponding plasma value.

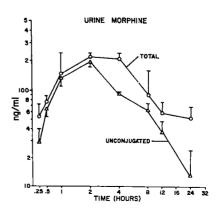
Discussion. Data show that morphine is rapidly absorbed from the epidural space

following which it is conjugated. Since the plasma free morphine fell below the minimal plasma analysic concentration at 2 hours, the long lasting analysia due to Duramorphis not caused by the presence of systemic morphine. Despite conjugation, the Cl of total morphine appeared slow. The appearance of conjugated morphine in urine was delayed for 2 hours probably because of the first-pass urinary elimination of free morphine. This may be related to augmented renal plasma flow in pregnancy.Contrary to popular belief, significant free morphine elimination occurs even after 24 hours in urine in obstetrical patients.

Table Plasma morphine pharmacokinetic data

	Free	Total
Vd _{ss} (L) t1/2beta (hours) C1(L/hours)	` ,	6 (0.9) 26 (7)
n=8, values in par	entheses represe	ent SEM.
References. 1. Kafer E et al: 418.	Anesthesiology	1982; 58:





TITLE: AUTHORS: AFFILIATION: NAUSEA AND VOMITING FOLLOWING AMBULATORY SURGERY: ARE ALL PROCEDURES CREATED EQUAL? AO Pataky, M.D., DS Kitz, Ph.D., RW Andrews, B.A., and JH Lecky, M.D.

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INTRODUCTION: Nausea and vomiting (N/V) are common postoperative complications which have been shown to prolong recovery room (RR) stay following diagnostic laparoscopy in day surgery unit (DSU) patients. Prolonged recovery may disrupt patient flow and will increase per patient institutional costs. The purposes of this study were 1) to assess our clinical impression that the incidence of N/V varies among surgical procedures, and 2) to examine RR time for patients with N/V.

METHODS: We examined the records of patients who received general anesthesia for the five most common procedures in our DSU in the period September 1984 to February 1985. The procedures included dental extraction (DEN), knee arthroscopy (KA), uterine dilatation and curettage (D&C), laparoscopy (LAP), and Laparoscopic ovum retrieval (OVUM). The following data were collected: patient demographic characteristics, anesthetic agents and adjuncts, duration of surgery, the occurrence of postoperative N/V, medications administered in the RR, and duration of RR stay. Patients undergoing each of the five procedures were evaluated separately. Significance was assessed by chi-square analysis, z-tests, and analysis of variance, and was accepted at p(.05.

RESULTS: The incidence of N/V for all patients was 29%. Among the five surgical procedures, however, there was a significant difference in the incidence of N/V (Table). Furthermore, there was a significant difference among the three gynecologic procedures, D&C, LAP, and OVUM in the proportion of patients with N/V (p<.001) and between LAP and OVUM patients (p<.05). For each procedure except DEN, patients with N/V had significantly longer RR stays than did asymptomatic patients (Table). Moreover, there is a significant difference among all procedures in duration of RR stay. For each procedure, there were no significant differences between symptomatic and asymptomatic patients with regard to age, gender, body mass index, or ASA physical status. All patients received nitrous oxide intraoperatively. There were no significant differences in the incidence of N/V among patients who received isoflurane, halothane, or enflurane without narcotics. The incidence of N/V was not significantly different between patients who received fentanyl or nalbuphine without inhalation agents, or among patients who received a combination of narcotic and inhalation agents. The incidence of N/V among patients receiving intraoperative narcotics (ION) was not significantly different from the incidence among those who did not receive ION. For each procedure, there was no difference in duration of surgery between symptomatic and asymptomatic groups. DISCUSSION: This study examined N/V following specific surgical procedures. While the overall rate of N/V is consistent with those reported by other authors, we found a significant difference in the incidence of N/V among the five surgical procedures. Depending on the procedure, 12 to 54% of patients experienced N/V. This suggests that evaluations of postoperative N/V should focus on

specific surgical procedures rather than on demographic characteristics or surgical specialty. We confirmed that N/V is associated with longer RR stays; RR stay was extended by as much as 56% for patients with postoperative N/V. For DEN, N/V may be stimulated by swallowed blood. Following emesis, patients may feel better and recover rapidly. Additionally, we observed a significant difference in RR times among the surgical procedures. Our findings suggest that patients receiving ION have a higher incidence of N/V than patients who do not receive an ION. Though the differences were not statistically significant, the trend is consistent with the findings of other authors regarding use of ION and N/V.2 The higher rates of N/V following use of ION may be clinically significant in terms of maximizing patient comfort and patient flow. This is particularly important in light of the extended RR stay associated with N/V. Prospective studies should examine factors that predispose patients to N/V such as use of nitrous oxide and ION, and prophylactic measures such as use of antiemetics. The differences in the incidence of N/V and in RR times for particular procedures suggest that these evaluations should focus on specific surgical procedures. The results from this study may be used to estimate sample sizes for these prospective studies. DSU administrators may also use these results to establish daily scheduling principles such as scheduling patients for procedures with higher incidences of N/V and longer RR times early in the day. Additionally, it may be desirable to have step down recovery units available for patients undergoing those procedures with higher incidences of N/V and prolonged RR stays.

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TABLE: NAUSEA AND VOMITING AND RECOVERY ROOM TIME

Procedure	DEN	KA D&C		LAP	OVUM
N	32	73	90	175	5 9
Mean RR Time in Hou: (SD)	rs				
No N/V	2.23 (.50)	1.87* (.53)	1.66* (.56)	2.21* (.63)	2.73* (.62)
N/V	2.32 (.55)	2.23 (.63)	2.46 (.86)	2.81 (.90)	3.45 (.85)
All Patients**	2.24 (.51)	1.94 (.57)	1.77	2.41 (.80)	3.10 (0.83)
2 N/V***	16	22	12	35	54
N/V per Technique No Intra-op Narc. Intra-op Narc.	12 33	17 37	11 17	30 42	52 60

*PC.05 for difference in RR time between patients with No N/V and N/V **PC.03 for difference in RR time amon all procedures ***PC.02 for difference in incidence of N/V among procedures

PATIENTS PRESENTING FOR HEPATIC TRANSPLANTATION: COMPARISON OF TYPICAL AND LOW CARDIAC

INDEX GROUPS

Authors:

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Introduction. The typical patient presenting for orthotopic hepatic transplantation has an elevated cardiac index and decreased systemic vascular resistance. Kang and Gelman stated that hepatic transplant patients with initially low cardiac outputs may experience unusual cardiovascular instability throughout the operative course. Similar impressions have been voiced by multiple centers involved in adult and pediatric hepatic transplantation, but no clinical data exists to substantiate these claims. The purpose of this study was to examine this subgroup of patients in an attempt to uncover the basis for these unsubstantiated claims, and to determine if they had an increase risk of poor outcome.

Methods. A retrospective review of 80 adult orthotopic hepatic transplant procedures, that routinely incorporated the use of veno-venous bypass, was undertaken in order to investigate a select subgroup with cardiac indices less than 2.8 liters/minute M². A matched group having typical cardiac indices, but the same preoperative diagnoses, were selected at random from the remaining patients for comparison purposes. All patients were managed according to the standard anesthetic protocol for this procedure at our institution. The initial cardiac outputs, those used for classification of patients, were obtained following induction of anesthesia. Routine montoring of these patients included: arterial pressures from radial or brachial arteries; measurement of central venous and pulmonary artery pressures, thermal dilution cardiac output. and core temperature from the Swan Ganz catheter; blood gases; electrolytes; glucose; serum osmolalities; colloid osmotic pressures; and coagulation profiles. Blood pressures, heart rate, cardiac outputs and temperature were plotted every 5 minutes on the anesthesia record during the procedure by computer. These data were used in the comparison of the groups. Preoperative laboratory data and intraoperative blood product utilization were reviewed, along with length of postoperatize ICU stay, duration of hospitalization following transplantation, total anesthesia time, and the duration of veno-venous bypass.

Results. The low cardiac index (LCI) group consisted of 11 patients with a mean cardiac index, following induction, of 2.19 1/min M2 (+ 0.54). An additional 11 patients, with mate ed preoperative diagnoses, had a mean cardiac index of 4.93 $1/\text{min}\ \text{M}^2\ (\underline{+}\ 1.24)$ and was significantly different from the FIgroup (P[0.001). Systemic blood pressures were not significantly different between groups, however systemic vascular resistance was significantly higher in the LCI group, as expected Four patients from the LCI group demonstrated unusually large variability in heart rate, systolic, mean and diastolic blod pressures when compared with other patients in the same group, and all patients in the typical cardiac index (TCI) group. Cardiac outputs obtained prior to, and following reperfusion of the homograft demonstrated a 90.9% (+ 52.2%) increase in the LCI group and a 96.7% (+ 77.2%) increase in the TCI group, that was not significantly different. Intraoperative arterial blood gases, acid-base status, and chemistries were reviewed. No significant differences could be demonstrated between ing parameters; K+, Na+, Ca++, PO2, PCO2, hematocrit, and serum osmolality. Colloid osmotic pressure was significanti7

increased in the LCI group, but only immediately following the discontinuation of veno-venous bypass. The pH was significantly higher only at the start of the procedure in the LCI group, while the corresponding base deficit was significantly higher in the TCI group. Intraoperative blood product utilization was not significantly different among groups. Length of time on veno-venous bypass, total anesthesia time, length of stay in the ICU, and length of hospitalization following transplant were also not significantly different. There was 1 intraoperative, and 1 postoperative, death in the LCI group. The TCI group had 2 postoperative deaths. In an attempt to determine the degree of liver dysfunction prior to transplantation, immediate preoperative values of prothrombin time, activated partial thromboplastin time, total bilirubin, SCOT, SCPT, albumin, amylase and glucose were compared among groups. No significant differences were uncovered.

Discussion. A subgroup of patients with endstage liver disease and atypically low cardiac indices, thought to present a difficult anesthetic course, have been described. The etiology of this low cardiac output state remains unclear, but may be related to the stage of the disease process. although not obvious from preoperative laboratory data. Vascular shunts thought to be responsible for low peripheral resistance, elevated cardiac output, and increased circulating blood volume in the typical patient, are probably not present in this group. Low cardiac outputs in the presence of normal peripheral vascular resistances and large vascular shunts would produce ischemia that could be demonstrated by increasing base deficits, inconsistent with the data presented here. The large variability in heart rate and arterial blood pressure, observed in 4 patients from the LCI group, may result from decreased venous blood volume which diminishes the effectiveness of cardiovascular control mechanisms. Another possible explanation for low cardiac output involves myocardial dysfunction, which may arise from circulating myocardial depressants or cardiomyopathies. Circulating myocardial depressants are not likely since, despite blood volume replacement and a functioning transplanted liver, cardiac output was never significantly different between the start and end of the procedure. In general, a failing myocardium is also not suspect, because the cardiovascular system responds with the same percentage increase in cardiac output in both the LCI and TCI groups upon reperfusion of the homograft.

Although 36 percent of patients with low cardiac indices demonstrated significantly greater heart rate and blood pressure variability, there were no other identifiable differences in their management or outcome when compared to typical hepatic transplant recipients. Therefore, in general, patients without documented cardiamyopathies, but with low cardiac indices in the presence of end stage liver disease, probably do not represent a contraindication to transplantation.

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MASS SPECTROMETRY AS A MORE COST EFFECTIVE GENERAL PURPOSE MONITOR THAN PULSE OXIMETRY

Authors:

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Introduction. Multiple sampling site mass spectrometry, and pulse oximetery, have been experiencing rapid acceptance by the anesthesia community. Within the current financial climate, the ability to obtain the most cost effective aid for anesthetic risk management provides a formidable challenge. The management of any particular general anesthetic may have associated with it, the optimum choice of monitors that will minimize the risk of anesthesia mishaps. However, it is desirable for each operating room to provide the same basic standard of patient care, with special purpose monitors available as needed for specific cases. The purpose of this work was to examine the relative merits and disadvantages of using the mass spectrometer or the pulse oximeter routinely during the administration of every general anesthetic.

Metrods. Data were collected from 4 Perkin Elmer Advantage systems in continuous use at our institution, and Nellcor and Ohmeda pulse oximeters. The 4 mass spectrometer systems monitored 50 operating rooms with a maximum of 13 rooms each.

Results. There are 3 popularly quoted disadvantages of the time shared mass spectrometer system: 1. Discontinuous monitoring since the machine is shared among several operating rooms; 2. Catastrophic failure resulting in the inability to monitor any patient connected to that system; 3. Cost. Data collected from 4 systems indicated that the mass spectrometer spent an average of 9.1 seconds (+ 0.73, n=85 patients) monitoring each patient, and 2.0 seconds (+ 0.11, n=85 patients) switching between rooms. No statistical differences could be found in these mean times when the data were grouped according to the number of rooms that were on line. Calibration required about 30 minutes, and was monitored daily for 1 month, then weekly for two months, on one system. Together with monthly data acquired from all 4 systems, the results indicated that the machine performed within manufacturers specifications when calibrated at 1 month intervals. Maintenance records for the 4 systems were reviewed, and indicated that an average of 2.5 hours were spent on servicing each system per year, when managed by an in-house biomedical engineering group. The total time, including calibration maintenance and repair, that the systems were unavailable for monitoring patients averaged 8.5 hours per system per year out of a possible 8760 hours per year (0.097%). Calibration and routine maintenance were always performed when the systems were not being used, limiting the total down time during patient monitoring to less than 37 minutes per system per year (worst case was 1.7 hours on one system). The hospital cost to provide monitoring is \$8.10 per patient based upon the actual number of patients being monitored, system amortization over 5 years, and the cost of maintenance, repairs, and calibration gases. From another perspective, the initial capital investment averaged approximately \$8,000.00 per room when the system was purchased in 1984, compared with \$5,800.00 per room for pulse oximetry during the same time period.

Pulse oximetry provides accurate information concerning oxyhemoglobin saturation under most circumstances. Since oxygen desaturation is not an early warming sign, but rather a terminal event, the major concern regarding pulse oximetry is whether there is enough time to recognize, identify, and resolve the problem in time to avert a catastrophic incident. Data were collected from 4 healthy volunteers who breathed oxygen concentrations from 0% to 100%. The time to reach 90%

desaturation while breath holding (at FRC) was recorded, along with the rate of saturation change. The time to reach 90% saturation, when using the rapid response mode and starting from 99%, ranged from 45 seconds at an FIO2 of 0 to greater than 4.5 minutes as the FIO2 reached 0.6. The subjects were unable to hold their breath much longer than 4.5 minutes, but as the FIO2 increased above 0.8, saturation remained at 100% to the end of breath holding. The rate of desaturation with an FIO2 of 0 was 72%/min and decreased to 6.7%/min at an FIO2 of 0.5 during breath holding at FRC.

Discussion. The advantages of the mass spectrometer are derived from the ability to display inspiratory and expiratory concentrations of simultaneously measured 02, 002, N2, N2O, halothane, enflurane, and isoflurane for each breath. In addition, display of the capnogram provides information concerning pulmonary pathology. Derived data such as A-a gradients and physiologic shunts are available when used with blood gas information. With constant ventilator settings, simple differences between inspired and exhaled concentrations provide relative 02 consumption (oxygen delivery) and Ω_2 production. The mass spectrometer has the unique ability to monitor the integrity of, and directly identify problems associated with: gas supply systems. anesthesia machine function, vaporizer and ventilator function, the patient circuit, as well as physiologic aspects of the cardiopulmonary system. Although the mass spectrometer provides detailed information that often enables rapid accurate trouble shooting of the problem, the amount of available information may be initially overwhelming. While connection to the patient and basic operations are trivial, full utilization of the instrument and subtle interpretation may require extensive training and/or experience. Distinct advantages of the pulse oximeter are: continuous monitoring except for movement artifact, electrocautery interference and peripheral vascular shutdown; and the ability to alert the anesthetist of impending disaster without complex interpretation of the displayed data or without close attention to the management of the anesthetic. Unfortunately, the oximeter only displays oxygen availability, unlike the mass spectrometer that indicates oxygen delivery (oxygen uptake). For simple problems associated with oxygenation of patients, such as airway disconnects, the pulse oximeter would probably be the last device to alarm following behind the ventilator, tidal volume monitor, airway pressure monitor, and the mass spectrometer. The pulse oximeter, in the case of more difficult problems, provides an alert of impending disaster without aiding in the identification of the cause, and possibly not in time to avert a catastrophic event. However, the pulse oximeter is the monitor of choice when desaturation is expected and the cause is known (i.e. bronchoscopy, one lung anesthesia,

The simplicity of the pulse oximeter is attractive, but since the device does not provide early warning or aid in the identification of the problem, routine use may not be justified. However, the mass spectrometer will detect decreased oxygen uptake before desaturation occurs and aid in the identification of the problem. Routine monitoring of the components of the anesthesia delivery system, in addition, may prove this to be a more cost effective general purpose monitor.

RELATIVE CARDIOTOXICITY OF IME LONG-ACTING LOCAL ANESTHETICS BUPIVACAINE AND

ROPIVACAINE IN DOGS

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Introduction. Potentially fatal cardiac arrhythmias have been associated with the accidental intravenous adminstration of some local anesthetic drugs (1,2). The principal objective of this study was to compare the cardiotoxicity of two long-acting local anesthetics, bupivacaine and ropivacaine [S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate], in pentobarbita-anesthetized, ventilated dogs. We also wished to examine the incidence of cardiac arrhythmias and the efficacy of resuscitative measures, including drag including drag interventions, cardiopulmonary resuscitation (CPR) or cardioversion techniques. potency ratio of 0.75:1.0 for bupivacaime versus ropivacaine was used in order to compare equianesthetic doses of the two drugs (3).

Methods. Briefly, adult mongrel dcgs
were anesthetized with pentobarbital amount instrumented to continuously monitor heart rate, arterial blood pressure, contractility and lead II ECG. After drug administratica, effective refractory periods (ERP's) were measured from ten randomly selected sites in the left ventricle via cardiac, plurge electrodes connected to a Medtronics programmable stimulator (4). Increased ERP dispersion, e.g. the difference between the longest and shortest ERP's, was considered to be a primary indicator of predisposition to reentrant ventricular arrhythmias. In addition, pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure and cardiac output were measured via a Swan-Ganz catheter coupled to a cardiac output computer (Edwards Laboratories).

Bupivacaine cr ropivacaine was administered as an intravenous bolus over one minute in cumulative doses of 2, 4, and 8 mg/kg or 2.66, 5.33 and 10.66 mg/kg respectively. A two hour recovery period was allowed between each injection. Plasma samples were taken ten minutes after each dose for analysis by gas chromatography.

TABLE 1: Cardiotoxicity of Intravenous Bupivacaine or Ropivacaine

Drug Bupivacaine 2.0 mg/kg 4.0 mg/kg 8.0 mg/kg	ERP Dispersion (msec) 13.75 ± 4.61 (8) 78.57 ± 13.88 (7) 95.00 (2)
Ropivacaine 2.66 mg/kg 5.33 mg/kg 10.66 mg/kg	11.43 ± 4.59 (7) 17.00 ± 2.60 (11) 56.67 ± 10.54 (6)

Data are mean ± SEM for (n) observations

Results. Both bupivacaine and ropivacaine
caused a dose-related increase in ERP
dispersion, measured within 2-5 minutes after the drug's intravenous administration (table 1). Most regions of the left ventricle showed prolonged ERP's, indicating slower conduction, but in some cases ERP's were unchanged or shorter than in control periods. Importantly, ERP dispersion was significantly greater for bupivacaine than ropivacaine after the second and third doses of local anesthetic. The incidence of cardiac arrhythmias was also higher for bupivacaine-treated animals compared to dogs given ropivacaine. Five of eight dogs experienced cardiac arrhythmias after the 8 mg/kg dose of bupivacaine and one animal developed an arrhythmia after 4 mg/kg, iv. In contrast, only four of ten dogs given an equianesthetic dose of ropivacaine (10.66 mg/kg) had cardiac arrhythmias, and none had arrhythmias after 5.33 mg/kg. Characteristic ECG changes associated with bupivacaine or ropivacaine administration included shortened R-waves, prolonged S-T interval, and, especially, increased area-under-the-curve of the T-wave. Plasma concentrations of these drugs, measured ten minutes after intravenous administration of the highest dose, were 20.48 ± 6.28 and 15.26 ± 5.04 ug/ml for bupivacaine and ropivacaine, respectively.

<u>Discussion</u>. In these experiments, bupivacaine was more likely than ropivacaine to produce cardiac arrhythmias at the highest dose administered. Bupivacaine caused arrhythmias in 75% of dogs tested, whereas only 40% had arrhythmias after ropivacaine. Lower doses of bupivacaine increased dispersion of ERP's in the left ventricle to a greater extent than ropivacaine, again indicating greater cardiotoxicity of bupivacaine. Resuscitative measures were equally successful in dogs experiencing cardiac arrhythmias due to bupivacaine or ropivacaine toxicity, with about 50% of animals recovering a stable rhythm and adequate blood pressure without metabolic acidosis. Hence, the long-acting local anesthetic ropivacaine appears to be less cardiotoxic than bupivacaine when administered in repeated, intravenous doses.

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CISTERNAL CSF MORPHINE LEVELS AND VENTILATORY DEPRESSION FOLLOWING EPIDURAL

ADMINISTRATION OF MORPHINE SULFATE IN THE AWAKE DOG

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Introduction. Delayed ventilatory depression has been observed in association with epidural (ED) and intrathecal (IT) administration of morphine (M) and has been ascribed to rostral spread of M within the spinal subarachnoid space (SAS) to brain stem respiratory centers However, controversy exists as to whether M concentration changes in cisterna magna (CM) CSF (taken to represent M levels at the brain stem) or ventilatory changes over time, following IT-M administration, are consistent with the rostral redistribution hypothesis (2,3,4). Reports relating M levels at the brain stem to ventilatory changes as a function of time following ED-M are absent from the literature. The present report describes the results of our investigation of the above employing an awake dog preparation.

Methods. Mongrel dogs (30 kg) were surgically prepared under general anesthesia with chronic indwelling femoral arterial and venous catheters, guide cannulae for insertion of spinal needles into the CM and 4th ventricle (V4), ED catheters (see ref. 5) and tracheostomy. Appropriate placement of the ED catheter (inserted 1-2 days prior to study) was demonstrated via fluoroscopy and, following recovery from anesthesia, by the rapid appearance of hindlimb paralysis upon lidocaine injection. Eight to 14 days were allowed for recovery from the other surgical procedures. For study, the dogs were placed in a stanction that provided comfortable head and body restraint and C M and V4 needles inserted. Following a 1 h control period, that included 6-7determinations of PaCO2 and 2 evaluations of ventilatory drive (VD), the dogs received an injection of 20 mg M sulfate plus [14 C]-M (in 3 ml saline) via the ED catheter. Arterial blood was sampled at 15 min intervals for analysis of PaCO2 and plasma 14C activity and VD evaluations performed every 30 min. CM-CSF was collected at 15 min intervals using continuous withdrawal at a rate (20-30 ul/min) that maintained V_{μ}^{u} pressure at 3-7 mmHg. Samples were analyzed for 14 C activity and M base concentration (via HPLC). VD assessments were done using a CO₂ rebreathing procedure and, to facilitate comparisons among dogs, were based on the 1 sec inspiratory occlusion pressure change (dp/dt) at a $PaCO_2 = 70 \text{ mmHg during}$

Results. In the figures, all values are expressed as means $\pm SEM$. As shown in fig. 1 (left), the ^{14}C activity in arterial plasma peaked at 30 min and declined to 20% of the peak value by 6 h. $CM-CSF^{14}C$ activity reached its peak level by 45 min and then declined steadily, but much more slowly than in arterial plasma, reaching 60% of the 45 min activity at 6 h. The 14 C activity represents M present as unconjugated M base plus conjugated M (principally M-3-glucuronide [M3G]). V4 administration of M (6), but not M3G (unpublished), depresses ventilation in dogs. The aims of the present study are therefore more accurately met through analysis of time-related changes in the levels of CM-CSF base. Levels of M base in CSF (fig 1, right) peaked at 45 min (at 64 ng/ml) declining gradually to 50% of the peak concentration at 6 h. Figure 2 shows that the maximal ventilatory depression was achieved by 1.5-2 h with no further depression occurring thereafter, although significant depression was maintained out to 6 h.

Discussion. The present finding of an early peak in CM-CSF M levels (45 min) followed by a steady decline thereafter does not appear consistent with a significant rostral redistribution of M within the SAS, following ED administration in the dog. It is more likely that the M presented to intracerebral sites was delivered via blood following its uptake primarily into the extensive ED venous system (1,5). The 1-2 h delay in the maximum ventilatory depression following the peak CM-CSF M base concentration is similar to previous findings in dogs given intravenous (IV) M (7). However, the present results of a slow decline in CSF M base levels and a ventilatory depression maintained over 6 h is in contrast to findings in IV-administered dogs where a far more rapid decrease in CM-CSF M (to <10% of peak at 6 h) and a return to nearnormal ventilation over 6 h were reported (7). significant differences in the pharmacokinetics and ventilatory pharmacodynamics when comparing ED and IV administered M.

FIGURE 1.

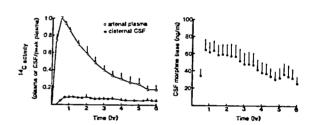
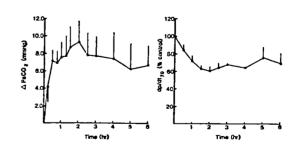


FIGURE 2.



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Title: SPINAL ANESTHESIA FOR OUTPATIENT SURGERY

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Introduction. Long a standard of safe anesthesia practice, spinal anesthesia(SA) has been singled out as an inappropriate anesthetic choice for day-surgery patients (1,2). These studies do not reflect our experience with post lumbar puncture (LP) complications. This prospective study was undertaken to determine outcome following SA in outpatients.

Methods. Following approval of appropriate institutional review boards, all patients electing SA from January 1, 1987 through May 30, 1987 were studied. Data collected at the time of operation included: age and sex of the patient, surgical procedure, anesthetic agent, site of LP, needle gauge, (25 or 26), number of attempts, experience of the anesthetist, and complications or failures. The patients were discharged to home only after all signs of the block had disappeared and the patient could void. Telephone inquiry was made between the third and twenty first postoperative day (median = 5 days) and the nature and degree of complaints including headache(HA), backache(BA), and urinary retention was recorded. The severity of HA was graded 0 to 4: 0 = no HA, 1 = mild, nonpostural HA, and 2 or greater = postural and of increasing severity (3). HA of 2 or greater was considered significant. An analogous score described BA severity. 0 = no BA, 1 = mild, lasting less than 24 hours, 2 = mild, lasting up to 48 hours, 3 = moderate lasting more than 48 hours, and 4 = severe for at least 24 hours. The need for an epidural blood patch to alleviate HA symptoms was also noted. The Chi Square test was applied for data comparison and the Yates correction was used where sample size dictated.

Forty four consecutive females receiving general anesthesia(GA) for laparoscopy were also studied. The incidence of nausea in the recovery room was recorded for these patients as well as their cohorts who received SA, additionally.

Results. Three hundred two patients received SA as outpatients, however 5 required GA and 9 couldn't be reached afterward. The remaining 288 patients consisted of 163 females (ages 14 to 72 years), and 125 males (ages 14 to 78 years). Table 1 outlines the distribution of surgical procedures.

Table 1

	ARTROSCOPY	LAPAROSCOPY	OTHER LITHOTOMY	OTHER SUPINE	OTHER PRONE
MALE	57	0	32	34	2
FEMALE	25	42	78	16	2

Overall incidence of HA was 11% with a significant difference in occurrence between males and females (p .005), (See Table 2). Incidence of nonpostural HA was identical for males and females (5.6%).

Table 2 HEADACHE DATA

	NO	GRADE	GRADE	GRADE	GRADE	(%) GRADE 2
	HEADACHE	1	2	3	4	or greater
MALE	113	7	3	2	0	4
FEMALE	127	9	12	6	9	16.6

There was no significant correlation between HA and the number of attempts, needle gauge, experience of the technician, or surgic. I procedure. No HA was reported in any patient greater than 55 years of age. Six (22%) of the females with HA required epidural blood patch. Patients receiving GA reported a 2.5 % incidence of nonpostural HA.

Table 3 BACKACHE DATA

	NO	GRALE	GRADE	GRADE	GRADE	(%) GRADE 2
	BACKACHE	1	2	3	4	or greater
MALE	87	9	21	8	0	23
FEMALE	86	12	48	12	5	40

The overall incidence of BA was 32% with females reporting a significantly greater incidence than males (p.005). Backache was not related to position, (lithotomy vs. supine), number of attempts, site of LP, or age. The incidence of BA was significantly less (10%) in patients who received GA (p.005).

The incidence of postoperative nausea in the recovery room in patients undergoing laparoscopy was 21% following SA and 68% following GA (p .005). No patient reported urinary retention.

Discussion. The results of this survey of 288 patients given spinal anesthesia for outpatient surgery are not in agreement with previous studies in outpatients. The males, particularly, had a much lower incidence of HA and BA in this study than the previously reported rates of 37% and 55%, respectively, (1). Backache was a frequent complaint, but it's noteworthy that only 5 patients described theirs as severe. The difference in complication rates after spinal anesthesia between males and females deserves further study. Spinal anesthesia should not be discarded from the anesthetic options suitable for outpatients, especially males.

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Title: PHYSIOLOGIC MONITORING FROM THE TRACHEA: DEVELOPMENT OF A MULTIMONITOR ENDOTRACHEAL TUBE

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Introduction. A novel approach to patient monitoring has been developed which allows collection of physiologic data from a single anatomic site - the trachea. Multiple sensors have been fashioned and attached to an endotracheal tube and tested in dog and sheep experiments. ECG, heart, breath and Doppler sounds, and temperature are monitored directly from the trachea via a cuffed endotracheal tube.

Methods. Nine dogs and 3 sheep were anesthetized and intubated with sensors fabricated on conventional endotracheal and jet ventilation tubes. Instrumentation included conventional surface-lead ECG, esophageal, pharyngeal, rectal, and Swan-Ganz® blood temperature. In select dog experiments, a percutaneous transluminal coronary angioplasy (PTCA) catheter was placed in the left anterior descending coronary artery with an aortic pressure catheter.

Results. A variety of ECG electrode placements on endotracheal tubes were evaluated to determine optimum electrode placement and interface site with the tracheal mucosa. A 3electrode system was developed which allowed ECG monitoring completely from within the trachea. Comparison with surface ECG signals demonstrated crisp ECG signals and clear P, QRS and T waves. Further comparisons illustrated increases and decreases in heart rate with surface warming and cooling of the dog, increases in heart rate with ephedrine injections, clear P waves monitored from the tracheal ECG during tachycardia not visible in the surface ECG, and evidence of ischemia on the tracheal ECG when the LAD coronary artery was occluded with a PTCA balloon.

Tracheal temperature was monitored from the endotracheal tube with a thermistor or thermocouple which paralleled conventional esophageal temperature measurements, both in the sheep and the dog (usually varying less than 0.4°C). The dog was utilized in most experiments because the anatomy more closely approximates the human. (Sheep studies required an extended length endotracheal tube.)

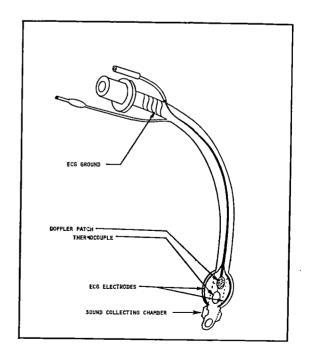
Heart and breath sounds could be monitored from various channels on the jet ventilation tube and from fabricated ports on the endotracheal tube (air transmission). A small audio amplifier placed distally on a pilot tube provided spectrally distinct bands for heart and breath sounds.

A Doppler crystal was placed on the tracheal cuff balloon and evaluated for monitoring of heart and breath sounds and as a detector for air embolism. In dog studies, heart sounds were clearly detected by the Doppler probe. By simply rotating the tracheal tube, either arterial or venous sounds could be

monitored (5-hour study period). Small increments of air (0.1 cc) injected into a forelimb vein were immediately amplified.

Discussion. A multimonitor endotracheal tube has been developed and tested in dogs and sheep which allows monitoring of ECG, temperature, and heart, breath and Doppler sounds from the trachea. The tracheal tube Doppler sensor has advantages over the conventional chest precordial or esophageal Doppler because of the absence of movement artifact and earlier detection for sitting neurosurgical cases because of the immediate air detection at the level of the superior vena cava. This concept of monitoring vital signs has immediate application for patients undergoing general anesthesia and surgery, for patients in a critical care unit, and emergency patient transport. Multimonitor endotracheal tubes can replace certain conventional monitors and are currently being fabricated for clinical trials.

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RESPIRATORY SINUS ARRHYTHMIA: AN INDEX OF ANESTHETIC DEPTH ?

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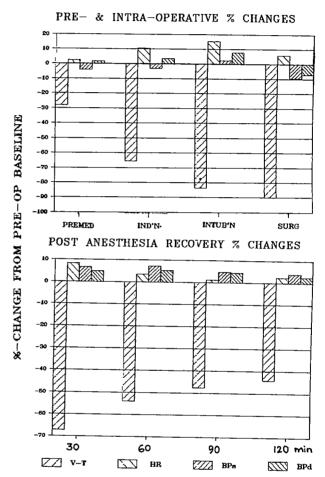
INTRODUCTION: Anesthesiologists are asked more and nore to care for sicker Patients as well as to respond to the demands for safer and more expeditious outpatient surgery. Within this context we hypothesized that using Respiratory Sinus Arrhythmia [RSA] a measure of vagal tone (1), would give a more precese way to monitor anesthetic depth and recovery. The vagal influence on cardiac rhythm can be extracted by computer analysis of the beat-to-beat variations in the routine ECG and affords a non-invasive "window" into CNS activity (2) that might consistently reflect the depressant effect of various anesthetic agents.

4ETHOD: The study protocol was approved by the Invesrigational Review Committee. Written informed consert vas obtained from all fourteen patients (ASA I or II, mean age 36 years). All patients, scheduled for elecive surgery, were premedicated with IM midazolam . (5 ${\rm ig/kg}$ and glycopyrrolate .2 mg and after pre-curarication induced with 4.5 mg/kg thiopental followed by 1.5 to 2.0 mg/kg succinylcholine to facilitate traheal intubation. Surgical anesthesia was maintained 7ith N2O 70% in O2 30% and enflurane 1 to 3%. Muscle relaxation was achieved with either vecuronium .1 mg/ ig or d-tubocurarine .3 mg/kg and later reversed with hysostigmine 2.5 to 5.0 mg and glycopyrrolate .5 tc .. 0 mg. Continuously recorded ECG data were analyzec m-line for RSA and heart rate [HR] using a Delta-Bimetrics Vagal Tone Monitor (3). Blood pressure [BP] as measured with DINAMAP. RSA, HR and BP were measued before and after premedication, during induction, ntubation and surgery, and during a two hour postperative recovery period. Analyses of variance were alculated to test the differences in RSA, HR and BF mong the pre-,intra-and post-operative phases. Reression analyses were used to evaluate the relationhip between total anesthesia exposure and subsequent ecovery of RSA.

ESULTS: Mean values and standard deviations of RSA vagal tone), HR and systolic BP are given in Table:

-	•	6	
	RSA [ln]	HR [bpm]	BP [mm Hg]
ASELINE	6.3 ± 1.2	85 ± 14	125 ± 18
REMEDICATION	4.6 ± 1.2	87 ± 13	120 ± 18
NDUCTION	2.4 ± 1.6	94 ± 12	121 ± 17
NTUBATION	1.2 ± 1.1	98 ± 16	128 ± 23
URGERY	0.6 ± 0.5	90 ± 11	113 ± 20
ECOVERY 30'	2.0 ± 1.2	92 ± 12	132 ± 23
ECOVERY 60'	2.8 ± 1.6	88 ± 13	134 ± 18
ECOVERY 90'	3.2 ± 1.9	86 ± 12	131 ± 19
ECOVERY 120'	3.4 ± 1.9	87 ± 14	130 ± 19

SA decreased markedly after premedication and during aintenance of anesthesia; it was depressed by 90% rom baseline during surgery. BP dropped by 8% during urgery, HR did not change significantly (Figure 1). uring recovery, RSA gradually returned to baseline ut remained depressed by 44% after 2 hours of recovery. HR and BP were within 10% of the pre-operative alues during recovery (Figure 2). Regression analyis showed a strong correlation between the total ansthesia exposure, defined as [vol% enflurane] x [exosure time], and the rate of recovery of RSA, with = 0.74.



DISCUSSION: Determining the depth of anesthesia has never been exact science. Commonly used signs such as patient's movement, HR, BP and pupilary changes are not reliable; multilead EEG analysis is expensive and difficult to interpret. The dose-related changes seen in RSA with premedication, induction and maintenance as well as recovery from enflurance anesthesia were demonstrated here to parallel the depth of anesthesia and the rate of recovery. Changes in HR and BP showed no such consistency. Thus monitoring RSA (vagal tone) provides a consistent single index to guide administration and recovery from enflurance anesthesia.

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Title: THE QUALITY OF EPIDURAL MORPHINE ANALGESIA FOLLOWING EPIDURAL ANESTHESIA WITH CHOLOROPROCAINE

OR CHOLOROPROCAINE MIXED WITH EPINEPHRINE FOR CESAREAN DELIVERY

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INTRODUCTION: Epidural administration of narcotics has become a common method of postoperative analgesia, particularly after cesarean delivery. However, when morphine is administered epidurally following epidural anesthesia with chloroprocaine, the onset of analgesia is delayed and its quality is poor, probably because of the acidity of chloroprocaine solution (1). When epinephrine is added to a local anesthetic, the acidity of the solution increases. If indeed the pH of the environment determines the quality of epidural morphine analgesia, then adding epinephrine to chloroprocaine should further reduce its quality. This study was designed to determine the effect of epinephrine on the quality of epidural morphine analgesia.

METHOD: The protocol was approved by the Hospital's Committee on Scientific Activities, and informed consent was obtained from the patients. Twenty patients, scheduled for cesarean delivery under epidural anesthesia, were studied. Ten patients received plain chlorprocaine 3% (CL group), and another ten patients received chlorprocaine 3% combined with epinephrine 1:200,000 (CLE group). After the baby was delivered, each patient received 5 mg of preservative-free morphine epidurally. The following data was collected: 1. Incidence of late onset. 2. Duration of analgesia (time to the first request for systemic analgesia). 2. Quality of analgesia at 0-4, 4-18, and at 18-24 hours after surgery. 3. Incidence of pruritus, and nausea and vomiting. The quality of analgesia was assessed by the patient, as follows: 0=none, 1=poor, 2=fair, 3=good, and 4=excellent. The results in the two groups were compared and analyzed using ANOVA and Chisquare methods. P values smaller than 0.05 were considered significant. The pH of the local anesthetic solutions was determined using the Beckman digital pH meter model no. 3500.

<u>RESULTS:</u> The results are summarized in tables 1-3. The incidence of late onset of analgesia was greater and its quality poorer during the first four postoperative hours in the CLE group. The pH of the CL and CLE solutions were 4.41 and 4.22, respectively.

	AGE	WEIGHT	HEIGHT	
CLE	28±5	145±15	63±1	
CL	27±2	146±17	63±2	
P	NS	NS	NS	
Table 1:	The age (in	years), w	eight (in	pounds),
and height	t (in inches), in the \circ	CLE and CL	groups.

	ANALGES	IA SCORE,	AT HOURS	
DURAT		4-18	18-24	
CL 20±	4 1.6±0.5	2.9±0.6	2.1±0.3	
	01 <0.01	NS	NS	
Table 2:	The duration	n (in hour:	s) and score	s of
analgesia	in the CLE a	and CL grou	ups.	

	LATE ONSET	PRURITUS	N&V	
CLE	10		0	
CL	4	1	i	
P	<0.005	NS	NS	
Table 3:	The incidence	of late or	nset.	
moderate-	to-severe prur	itus, and	noderate	e-to-severe
nausea an	d vomiting (N&	V) in the (CLE and	CL groups.

DISCUSSION AND CONCLUSIONS: The greater acidity of chloroprocaine-epinephrine mixture apparently causes a greater degree of ionization of morphine molecules, and slows down their diffusion through spinal cord membranes (1). Our observations support the hypothesis that acidic environment inhibits epidural morphine analgesia. Although epidural morphine analgesia lasted longer in the presence of epinephrine, the onset of the analgesia was delayed and its quality during the immediate postoperative period was diminished. Although the mechanism of action of epidural opiates differs from that of local anesthetics, it seems that both groups are inhibited in acidic environment, probably due to greater electrolytic dissociation of their molecules (2).

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TITLE:

THE QUALITY OF EPIDURAL MORPHINE ANALGESIA FOLLOWING EPIDURAL ANESTHESIA WITH

LIDOCAINE OR CHLOROPROCAINE FOR CESAREAN DELIVERY

AUTHORS:

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INTRODUCTION: Epidural administration of narcotics has become a common method of postoperative analgesia, particularly after cesarean delivery. However, when morphine is administered epidurally following epidural anesthesia with chloroprocaine, the onset of analgesia is delayed and its quality is poor (1). Our study was designed to compare the quality of epidural morphine analgesia following epidural anesthesia with lidocaine to that following epidural anesthesia with chloroprocaine for cesarean delivery.

METHOD: The protocol was approved by the Hospital's Committee on Scientific Activities, and informed consent was obtained from the patients. Twenty patients, scheduled for cesarean delivery under epidural anesthesia, were studied. Ten patients received chloroprocaine 3% (CL group) and another ten received lidocaine 2% (LI group). Epinephrine 1:200,000 was added to the local anesthetic in both groups. After the baby was delivered, each patient received 5 mg of preservative-free morphine epidurally. The following data was collected: 1. Incidence of late onset of analgesia. 2. Duration of analgesia (time to the first request for systemic analgesia). 3. Quality of analgesia at 0-4, 4-18, and at 18-24 hours after surgery. 4. The incidence of pruritus, and nausea and vomiting. The quality of analgesia was assessed by the patient, as follows: 0=none, 1=poor, 2=fair, 3=good, and 4=excellent. The results in the two groups were compared and analyzed using ANOVA and Chisquare methods. P values smaller than 0.05 were considered significant. The pH of the local anesthetic solutions was determined using the Beckman digital pH meter model no. 3500.

RESULTS: The results are summarized in tables 1-3. The groups were similar in age, height, and weight. There were no differences between the groups in duration of analgesia or side effects. However, the incidence of late onset of analgesia was greater and its quality was poorer in the CL group than in the LI group. The pH of the chloroprocaine and lidocaire solutions were 4.22 anc 6.42, respectively.

		AGE		WI	GIGHT .	HEIGH	ΙΤ	
CL		28±5		14	¥5±15	63±1		
LI		27 <u>±</u> 3		15	51 <u>±</u> 20	63±2	2	
P		NS			NS	NS		
Table	1:	The	age	(in	years),	weight	(in	pou

Table 1: The age (in years), weight (in pounds), and height (in inches) in the CL and LI groups.

		ANALGESIA	SCORE, A	T HOURS	
	DURATION	0-4	4-18	18-24	
CL	27±2	1 <u>±</u> 0	3.2 ± 0.6	2.5 ± 0.5	
LI	28±5	2.7±0.5	3.7±0.5	3.1 ± 0.7	
р	NS	<0.001	0.06	<0.05	
Tabl	le 2: The	duration (in hours)	and scores	of
epic	dural morph	ine analge	sia in th	e CL and LI	groups.

	LATE ONSET I	RURITUS	N&V
CL	9	2	0
LI	0	4	1
р	<0.001	NS	NS
Table	3. The incidence	of late	onset.

<u>Table 3:</u> The incidence of late onset, moderate-to-severe pruritus, and moderate-to-severe nausea and vomiting (N&V) in the CL and LI groups.

DISCUSSION AND CONCLUSIONS: The onset of epidural norphine analgesia is delayed and its quality is poor following epidural anesthesia with chloroprocaine. A possible explanation for this antagonism between morphine and chloroprocaine is the acidity of the chloroprocaine solution (1). The low pH possibly increases ionization of morphine molecules and thus slows their diffusion through spinal cord membranes. This is similar to the effect of acidity on nerve block by local anesthetics: The greater the acidity of the environment the slower the onset of the nerve block (2). It seems that although their mechanism of action is different, both epidural opiates and epidural local anesthetics are inhibited in an acidic environment.

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CONTINUOUS INFUSION EPIDURAL ANALGESIA IN LABOR:

THE EFFECT OF ADDING SUFENTANIL TO 0.125% BUPIVACAINE.

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Introduction. Previous studies have reported that analgesia for labor is improved when fentanyl is added to epidural bupivacaine (1, 2). Sufentanil has physical properties, such as high lipid solubility, and an increased affinity for the mu opiate receptor which suggest that it may be superior to fentanyl for epidural use (3). This study was done to examine the effect on quality of analgesia when sufentanil is added to an epidural infusion of bupivacaine.

Methods. Approval by the Human Subjects Investigation Committee and informed consent from the patients were obtained. Forty women in labor at term were randomly allocated to two equal groups. Patients had an epidural catheter placed at the second or third lumbar space, and received 10 ml of analgesic solution. Group 1 received 0.25% bupivacaine. Group 2 received 0.125% bupivacaine with sufentanil 2 ug/ml. At thirty minutes following the initial epidural injection both groups commenced an epidural infusion at a rate of 10 ml/hr. Group 1 received 0.125% bupivacaine while Group 2 received 0.125% bupivacaine with sufentanil i ug/ml. Return of pain was treated by 5 ml injections of analgesic solution as follows; Group 1: 0.25% bupivacaine, Group 2: 0.125% bupivacaine with sufentanil 2 ug/ml. Side effects were noted and degree of motor block was recorded. Analgesia was assessed by the patient on a visual analog pain scale (VAPS) during labor, and on a four point scale for delivery. Maternal and cord blood samples were taken at delivery for estimation of plasma sufentanil levels by radioimmunoassay.

Results. Patients in the two groups were comparable in age, parity, height, weight, cervical dilatation, initial VAP score and time interval from epidural placement to delivery. Sufentanil treated patients had lower mean VAP scores in labor than patients in Group I (see table). Analgesia for delivery was also improved, as more patients in the sufentanil group claimed to have complete analgesia. In addition more patients in the sufentanil group had no epidural 'top up' injections. Motor block was more common and more marked in Group I patients. Ten patients in Group 2 developed mild pruritus. No neonatal depression was apparent in either group of neonates and sufentanil plasma levels in mother and fetus at delivery were undetectable.

<u>Discussion</u>. These results demonstrate a significant improvement in analgesia for both labor and delivery when sufentanil is added to 0.125% bupivacaine infusions. An additional advantage of this technique is a reduction in the number of repeat epidural injections required. The only side effect observed in the mother was mild pruritus, and no neonatal depression was seen.

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QUALITY OF ANALGESIA FOR LABOR AND DELIVERY AND REQUIREMENTS FOR REPEAT EPIDURAL INJECTIONS

	Group 1 (Bupivacaine)	Group 2 (Bupivacaine/ Sufentanil)
Mean VAP score in labor	15.2 ±13.3	3.9 ± 9.7
Analgesia for delivery Grade 2 (good) Grade 3 (complete) b	11 7	3 16
Repeat epidural, injection	ns	
No injections D	5	12
One injection	11	5
Two injections,	2	3
Three or more		
injections	2	0

a p < 0.01, b p < 0.05

TITLE:

USE OF SOMATOSENSORY EVOKED RESPONSES FOR DETECTION AND PREVENTION OF NERVE

INJURY DURING TOTAL HIP ARTHEOPLASTY

AUTHORS:

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Introduction: The incidence of postoperative sciation nerve palsy (PSNP) following total hip arthroplasty (THR) is reported as 0.7-7.0% (1). The incidence at our institution is approximately 2.6%, and has been found to be more likely in women and in patients who have undergone previous surgery on the same hip (2). Stone et al (1) utilized cortical somatosensory evoked potentials (SSE= during THR and found that 20% of patients had intraoperative changes indicative of compromise in sciatic nerve function. The purpose of our investigation was : compare the incidence of PSNP in patients with and without intraoperative monitoring of SSEP, and to further determine the factors associated with both PSNP and intraoperative changes of SSEP which might indicate ner-e injury.

Methods: After obtaining informed consent arc intitutional approval, 72 adult patients (ASAII-III) scheduled for elective THR were randomly allocated to either monitored (I) or unmonitored (II) groups. Anesthet.c management consisted of N20 60-70% in oxygen. isoflurane, fentanyl, and pancuronium. Intra-arterial blocc pressure, central venous pressure, end-tidal CO2, oxyg∈L saturation, and temperature were monitored continuous and kept at stable levels in all patients during SSEP signa. acquisition. SSEP's were recorded using a Cadwell 8400 signal averager, with percutaneous stimulating electrode: placed over the peroneal nerve at the fibular heac bilaterally. Random stimuli were delivered at 3X motor threshold at a rate of 4-7 per second. Subdermal need ϵ recording electrodes were placed at C2 and 2 cm posterior to CZ, referenced to FPZ. Filters were set at 10 Hz arc 300 Hz. 250 stimuli were averaged per response, and two consecutive responses were averaged for each determination. Latency (ms) of the P1 cortical response and amplitude (uv) of the P1-N1 response were tabulated at 6 times during the procedure: after stable levels of anesthesia were obtained (BAS), after dislocation of the har (DIS), during reaming of the acetabulum (ACE), during femoral preparation (FEM), after relocation of the ha (REL), and during skin closure (CLO). Latency prolongation of >10% of baseline latency and/or amplitude reduction cf >50% of baseline amplitude were used as criteria for indication of sciatic nerve compromise. The response from stimulation of the contralateral peroneal nerve was used as control. Data from each group were compared utilizing stepwise discriminant analysis.

Results: Patient groups cid not differ in age, sez, weight, diagnosis, surgical approach, type of arthroplasty performed, or presence of previous surgical procedures cm the same hip. No factor was significantly associated with the presence of intraoperative SSEP change, although changes tended to be more common in women who had previous surgery. One of 40 patients in the unmonitored group (2.5%) sustained permanent PSNP, and one patient in the monitored group (3.1%) had transient PSNP that resolved within one week (Fig. 1). 41% of patients in the monitored group had a total of 23 changes in SSEP intraoperatively. Of these changes, 4% occurred during dislocation, 26% during acetabular reaming, 22% during femoral preparation, 35% during relocation, and 135 persisted at closure. 35% of these events were changes in latency only, and 43% were changes in amplitude (Fig. 2. Five events in four patients involved both latency prolongation and amplitude reduction (three during reduction, one during femoral reaming, and one persisted

at closure). In each case, the SSEP was completely abolished (flat). Three patients recovered SSEP after modification of the operative approach. The patient with persistent absence of the SSEP at closure awoke with PSNP (foot drop).

Discussion: The peroneal division of the sciatic nerve is most commonly involved in PSNP, and therefore was chosen for stimulation. Sciatic nerve ischemia due to stretching or compression is the most likely cause of PSNP. Our results indicate that stretching caused by reduction of the hip or retractor placement was more likely to cause alteration of SSEP, although SSEP changes were noted throughout the operative course. We were unable to demonstrate a statistically significant change in the incidence of PSNP by monitoring peroneal SSEP. However, the incidence of PSNP is low, and will require study of a larger patient population to clarify definite effects. Of the patients sustaining PSNP, one was unmonitored, and one displayed persistent significant abnormality of the SSEP (flat) that was unresponsive to surgical investigation and manipulation. A significant percentage of our patients appear to have intraoperative changes in SSEP that might indicate sciatic nerve injury. This is in agreement with the results of Weber, who found a 70% incidence of postoperative EMG abnormalities after THR (3). At present, we are unable to identify preoperative factors or intraoperative events that reliably predict SSEP change or vulnerability to PSNP. Experience in monitoring SSEP during spinal surgery indicates that persistent absence of serious abnormality of SSEP at the end of surgery predicts postoperative neurologic function (4), and our results support this. Monitoring of sciatic nerve function during THR may therefore be beneficial in detection of intraoperative nerve compromise that may result in postoperative sciatic nerve palsy.

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GROUP	AGE	SE) F	(%) M	HT (KG)	FREV SURG (%)	PSNP(%)
(TINOM) I (SE#M)	54.9	59	41	72.8	47	3. 1
SSEP CHANGE (N=13)	51.7	63	31	71.7	62	7.7
NO SSEP CHANGE (N=19)	57. 1	58	42	73-6	37	0.0
II (UNMONIT) (N=40)	59.6	48	52	78.6	38	2.9

FIG. 1: MONITORED VERSUS UNMONITORED PATIENTS UNDERGOING THR

TYPE SSEP CHANGE	DIS	ACE	FEM	RED	CLO	TOTAL(X)
AMPLITUDE (50%	1	4	3	2	6	18(42)
LATENCY) 18%	ø	2	1	3	2	8 (35)
вотн	0	ø	1	3	1	5(22)
TOTAL	1 (4%)	6 (26%)	5 (22≭)	(35≽:	(13≭)	53

FIG. 2: INTRAOPERATIVE SSEP CHANGES IN PATIENTS UNDERGOING THA

FETAL EFFECTS OF INDUCTION AGENTS IN THE HEMORRHAGED MATERNAL EWE Title:

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Introduction. Sodium thiopental (STP) and ketamine (KET) are used for induction of anesthesia in pregnant patients after acute hemorrhage. However, there is little information upon which to base the choice of anesthetic agent. Previous work has shown that the fetal response to decreased placental perfusion produced by maternal uterine artery constriction includes bradycardia, hypertension, elevated catecholamine levels and increased cerebral blood flow (1). Fetal response to maternal hemorrhage has been studied in less detail and organ blood flow changes have not been evaluated (2). The stress response to hemorrhage may be adversely modified by induction of maternal anesthesia. KET may support maternal and fetal blood pressure, maintaining placental perfusion and fetal cerebral perfusion. On the other hand, STP may reduce fetal cerebral metabolic rate and be "protective". Thus, this study was designed to examine the cardiovascular, metabolic and regional organ and cerebral blood flow responses of the sheep fetus to maternal hemorrhage when maternal anesthesia is induced with STP or KET.

Methods, Pregnant ewes (N-15) were anesthetized with halothane for the placement of femoral and carotid arterial catheters, femoral vein and pulmonary arterial catheters. Fetuses were exposed through a hysterotomy for placement of EKG elect-odes, femoral and brachial arterial catheters, femoral vein catheters and sagittal sinus catheters. Studies were performed after 72 hours of recovery. At the beginning of the study period, ewes were given 100 % oxygen for a 30 minute control period, then hemorrhaged 21ml/kg over 30 minutes. Animals had been previously randomized to one of three groups. Anesthetized animals received either STP (6.6mg/kg) or KET (13.2 mg/kg) with tracheal intubation facilitated by succinylcholine (1mg/kg). Control animals were observed after hemorrhage without anesthesia or intubation. The doses of STP and KET were selected based on results of a pilot study that demonstrated requirements of 11mg/kg of STP and 22mg/kg of KET to abolish the response to pain in normovolemic sheep. Hemorrhage has been shown to reduce drug requirements by approximately 30% in pigs(3). Accordingly, reduced doses were selected for this study. Fetal and maternal cardiovascular parameters were measured every 5 minutes during hemorrhage, then every minute during induction of anesthesia and there after until the end of the study. Maternal and fetal blood gases and fetal regional blood flow parameters, using radiolabeled microspheres, were measured before hemorrhage, after 15 and 30 minutes of hemorrhage, and 2 and 7 minutes after induction of anesthesia (STP or KET) or during post-hemorrhage observation (control group).

Results. Hemodynamic data has been collected in 5 control, 5 KET and 5 STP animals. Regional blood flow has been measured in 4 control, 5 KET and 5 STP fetuses. In these animals (N=15), hemorrhage produced a significant decrease (p<0.05) in maternal MAP from 103.3±9.3 torr to 54.8±torr (mean±SD), without maternal acidosis. Fetal responses included a significant decrease in pH and arterial oxygen content, and significant increase in blood flow to the heart, brain and adrenal glands (P<0.05). A decrease in fetal heart rate was observed, but with considerable variation.

In the control group (N=4), the fetuses sustained the increased blood flow to the heart, brain and adrenal glands in the 15 minutes flowing hemorrhage. Fetuses in both KET and STP groups showed a wide variation in response to induction and intubation. Following induction, fetuses in the STP group (N=5) had an increase in the heart rate which was not seen in the other group. Further, there was a sustained increase in myocardial and adrenal blood flow, but not cerebral blood flow, in the period after induction. Two fetuses in the KET group experienced cardiovascular and metabolic collapse following induction while the other three maintained increased organ blood flows. There were fetuses in all groups which demonstrated a progressive decline in fetal pH and hemodynamic values after hemorrhage. This deterioration correlated with low maternal arterial pressures. The control animals consistent response to hemorrhage (increased organ and brain blood flow) was in marked contrast to the variation seen after induction of anesthesia with STP and KET.

Discussion. Our results document that a maternal hemorrhagic stress produces alterations in fetal regional blood flow and acid-base status similar to those produced by placental insufficiency or maternal hypoxia. The increased blood flow to the brain and heart that occurs with hemorrhage may serve as a protective mechanism. Neither KET (13.2 mg/kg) nor STP (6.6 mg/kg) maintains these changes as well as no anesthesia. KET does not appear to provide any clear benefit despite the traditional assumptions concerning shock and anesthesia. These preliminary data, however, do not allow for formal conclusions regarding the specific effects of STP or KET on the sheep fetus stressed by maternal hemorrhage. Additional investigation using this protocol is in progress and completion of this study will allow a more detailed presentation of organ and cerebral blood flow following anesthesia induction.

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TITLE:

EFFICACY OF VECURONIUM BY CONTINUOUS INFUSION WITH EITHER ISOFLURANE OR FENTANYL-NITROUS OXIDE

ANESTHESIA

AUTHORS:

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INTRODUCTION: Vecuronium is a nondepolarizing neuromuscular blocker with an intermediate duration of action and minimal cumulative properties. These features make it suitable for administration by continuous infusion. This study was undertaken to establish and compare the infusion rate of vecuronium for a 90% depression of evoked EMG in patients receiving either nitrous oxide and narcotic as their main anesthetic or isoflurane.

METHODS: Following Institutional Review Board approval, informed consent was obtained from 19 ASA Class I-III adult general surgical patients free of neuromuscular, hepatic or renal disease and scheduled for elective surgery estimated to require at least 120 minutes of neuromuscular Patients were randomized into two blockade. groups to receive either nitrous oxide - fentanyl - isoflurane (0.5 - 1.5% inspired - Group I) or nitrous oxide - fentanyl (1 - 5 mcg.kg. $^{-1}$ hr. $^{-1}$ -Group F) for the maintenance of general anesthe-The unencumbered arm was immobilized and sia. used for evoked EMG monitoring of neuromuscular transmission using a Puritan Bennett AB-100 Anesthesia Brain Monitor^R. For induction each patient received sodium thiopental 4 - 6 mg.kg-1. The EMG was then calibrated and a stable baseline obtained. A bolus dose of vecuronium 0.08 mg kg-1 was administered and the trachea intubated when T_{I} of the evoked EMG reached 10%. Spontaneous recovery of neuromuscular blockade was allowed to occur until T1 returned to 10% of control at which time an intravenous infusion of vecuronium (200 mcg.ml⁻¹) was started. The initial infusion rate was 1 mcg.kg. - min - 1. The infusion rate was then manually adjusted in order to maintain T1 at 10 ± 2% of control. The infusion was stopped 20 mins. prior to the anticipated completion of surgery. Antagonism of neuromuscular blockade was accomplished with neostigmine (and atropine) when either T_1 or the T_4/T_1 ratio was less than 70% of paseline.

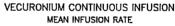
Comparison of infusion rates between groups was performed using analysis of variance. An average infusion rate was also calculated for each patient by dividing the amount of vecuronium infused by the duration of the infusion. A comparison is reported as statistically significant if p≤.05. Values are reported as the mean \pm standard deviation.

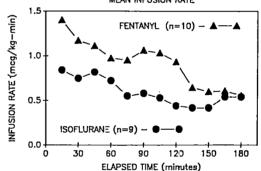
<u>RESULTS:</u> The T₁ was maintained at 10.8 \pm 4.1% in group F and 10.8 \pm 4.3% in Group I. The duration of infusion in Group F was 157.6 \pm 57 minutes and in group I 135 \pm 82 minutes. There was a significant difference between infusion rates required to maintain 90% depression of evoked EMG in Group F as compared to Group I (p=0.02). In Group F there was a significant decrease in infusion rate with time (p=0.02). The average infu

sion rate in Group F was $57.2 \pm 13.8 \,\mathrm{mcg.kg.^{-1}hr.^{-1}}$ and $42.4 \pm 11.9 \,\mathrm{mcg.kg.^{-1}hr.^{-1}}$ in Group I (p<0.05). The infusion rates for Groups F and I with respect to time are shown in Figure 1. Figure 2 is the combined infusion rates for both groups with the 95% confidence intervals.

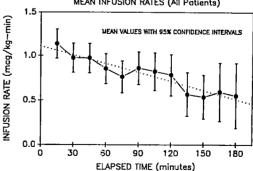
All patients were readily reversed with neostigmine and atropine and no episodes of recurarization occurred.

DISCUSSION: This study demonstrated that when an infusion of vecuronium is used in combination with isoflurane the infusion rate is 25% less than the infusion rate with a nitrous oxide-narcotic anesthetic. When a vecuronium infusion is used with fentanyl-nitrous oxide the infusion rate needs to be decreased with time. This suggests that vecuronium by continuous infusion shows cumulative properties.





VECURONIUM INFUSIONS MEAN INFUSION RATES (All Patients)



REFERENCE:

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Title:
Authors:

Continuous trending of fick variables in i.c.u. patients: A role for \dot{v}_{0}

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INTRODUCTION Continuous measurement of mixed venous oxygen saturation (SvO2) is commonly used as a monitor in critically ill patients. It is thought in most situations to reflect the balance of delivered and consumed oxygen (DO2 and VO2) but is sometimes misleading (e.g. sepsis) and unable to predict either parameter with certainty. The Fick equation describes, and recent experimental data supports a positive and perhaps linear correlation between DO2 and VO2 in certain groups of critically ill patients. This would imply a relatively fixed oxygen extraction ratio and rather narrow range of SvO2 values in these patients. Technologic advances now allow the continuous direct measurement of VO2 and arterial oxygen saturation (SaO2). We independently measured all components of the Fick equation simultaneously at regular intervals in heodynamically stable, post-operative patients who were mechanically ventilated in order to define their baseline variability and correlated changes between these variables in a clinical setting.

METHODS Following approval by the Institutional Review Board, ten patients admitted to the surgery-anesthesiology intensive care unit following major abdominal or thoracic procedures were studied on fourteen separate occasions for periods of not less than 3 hours. All patients were mechanically ventilated and oxygen consumption was measured using an Engstrom Metabolic Computer in conjunction with an Erica ventilator and Eliza MC CO2 analyzer (Gambro-Engstrom, Sweden). The equipment was initially tested in vitro using nitrogen dilution and methanol combustion to validate VO2 and RQ measurements respectively. We found VO2 measurements to be accurate (+/- 6%) with excellent reproducability (coefficient of variation = 2.7%). Arterial and mixed venous oxygen saturations were monitored using a pulse oximeter (Nelcor) and pulmonary artery catheter (American Edwards) respectively. Initial calibration of the catheter oximetric PA catheter as well as hourly hemoglobin (Hgb) determinations and accuracy checks of the oxygen saturation were performed using an IL 282 CO-oximeter (Instrument Laboratories). Recalibration of the oximetric PA catheter was performed for any drift greater than 2%. Cardiac output determinations were averaged from three measurements made by thermodilution technique (COtd) at end expiration (SAT 1 Oximeter/C.O. Computer, American Edwards). Coincident measurements of SaO2, SvO2, COtd, and VO2 (mean value over 4 minutes) were made every 15 minutes during the study period. DO2, oxygen extraction ratic (OER), and CO (COc) were calculated for each observation according to formulas outlined in Table 1. Correlations of variables were analyzed by simple linear

RESULTS The ten patients studied were comprised of 7 men and 3 women with a mean age of 65.1 years (range 32-82) and mean weight of 83.8 kg. (range 65-111). Over 200 discrete sets of data were collected representing greater than 50 hours of observation. Table 2 summarizes the measured and calculated data for all subjects. When each Fick variable was examined separately for its ability to trend COtd, VO2 exhibited a degree of correlation close to that of COtd (r=.78).

DISCUSSION This study demonstrates the utility of continuously tracking the three determinants of CO as derived from the Fick equation. We, like Davies et. al. 4,

found that CO calculated from independently measured variables correlates well with COtd in a clinical setting (r=.84). It is important to note that we did not consider dissolved O2 in our COc. Its contribution to arterial O2 content with paO2's maintained 150 would have averaged 3%. This relatively stable group of post-operative patients were found to exhibit a linear relationship between VO2 and COtd. While this may be partly due to the adequate cardiac reserve and intact microcirculation of these patients reflected in their hemodynamic stability, it suggests that VO2 may prove to be a useful continuous monitoring tool. It is worth noting that SvO2 correlated poorly with COtd. Finally, the relationship between VO2 and DO2 also appears to be linear in this group of post-operative ICU patients, adding to a growing list of disease entities including ARDS, COPD, and acute GI bleed in which this has been found to be true. The independent manner in which each parameter was measured makes mathmetical coupling of data less likely to be responsible for this relationship. Whether this linearity signifies underlying tissue hypoxia or represents a normal exercise response of a healthy cardiovascular system to increased demands must still be clarified. Many investigators believe that reduced VO2 is a primary event in shock states with the degree of depression correlating with mortality. They argue that therapeutic intervention should be aimed at improving DO2 and hopefully VO2. If this is true, then continuous monitoring of VO2 may prove valuable in both understanding shock states and managing these patients. Hopefully, this study will serve as a starting point to investigate these relationship with direct. continuous measurements in classes of hemodynamically unstable patients.

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Table 1	
DO2=COtd x Hgb x SaO2 x 13.4	
$CO\ddot{c}=\dot{V}_{O_2}/((SaO_2-SvO_2)\dot{x} \text{ Hgb x } 13$ $OER=\dot{V}_{O_2}^2/DO_2$	3.4)
OFR=V-2/DO-	•

<u>Table 2</u>				
	mean	s.d.	range	r values
DO ₂ *(ml/min)	878	336	469-1998	.80(DO ₂ -VO ₂)
VO2(ml/min)	274	80	150-154	.78(COtd-vog)
COfd(1/min)	5.9	2.0	2.8-14.2	.80(DO ₂ -VO ₂) .78(COfd-VO ₂) .84(COfd-CO _c)
CO _e *(1/min)	6.2	2.1		e e
SvO _{2(%)}	72.2	4.2	62-82	10(COtd-SvO ₂₎
SaO2(%)	98.7	1.8	93-100	2.
Hgb(g/dl)	11.7	1.4	8.8-15	
OER*	.30	.06	.2040	
				*calculated

.4.

TITLE: POSTPARTUM PLASMA ADH AND BETA ENDORPHIN LEVELS FOLLOWING DURAMORPH

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Introduction. The cephalad spread of epidural morphine (Duramorph) reportedly produces ADH release in non- pregnant subjects. No data are available in pregnant patients. We studied the effects of Duramorph on anterior and posterior pituitary function using plasma immunreactivity of ADH and beta-endorphin (B-E) in patients given Duramorph for postoperative analgesia following elective cesarean section under lumbar epidural anesthesia (LEA).

Methods. The study was approved by the Human Research Review Board. The patients gave informed consent. Following I.V. infusion cf 1200 ml of crystalloid, LEA was induced to T4 level with lidocaine 2% with 1:200,000 epinephrine. Group I (n = 12) received 5 mg Duramorph immediately after delivery. Maternal venous blood samples were obtained before , and at 0.5 , 2 , 4 , 6 and 24 hours after Duramorph. In Group II (n = 10) , Duramorph was administered 4 hours after delivery with postoperative analgesia being maintained during that time with 0.25 % bupivacaine infusion. Measurements were made before ,and at 0.5 , 2 , 4 hours after delivery and 0.5, 2, 4 and 24 hours after Duramorph. Plasma ADH, B-E, total morphine, and serum osmolarity were measured. No other medications were given during the study period . Two patients from each group were omitted from the study because of unusually high levels of ADH (200-300 fold increase) between 2 to 4 hours after delivery. The results from the remaining patients in the two groups were expressed as mean + SE and analyzed with analysis of variance (ANOVA), correlation and t - test .

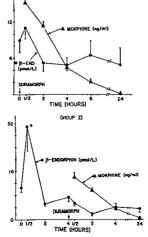
Results In both groups, plasma morphine levels peaked at 0.5 hour (Figs 1 and 2). Plasma ADH did not significantly vary from the baseline at different time periods (Table 1). Group I: Plasma B-E showed a steady decline from the baseline values over the study period. (Fig 1). Group II: A significant 3-fold rise (F = 7.62, p 0.05) in plasma B-E was observed at 0.5 hour after delivery, with subsequent steady decrease (Fig 2). Following Duramorph, a further significant decrease occurred in B-E. In both groups, serum osmolarity did not correlate with ADH levels in the first 12 hours. (Table). Plasma ADH and B-E did not correlate significantly with each other in both groups.

<u>Discussion</u> Data show that in some patients high ADH levels do occur following delivery regardless of Duramorph. The reason for this is unclear. The absence of a

significant rise of B-E in Group I suggests attenuation of stress by the high levels of serum morphine. The steady decline in B-E in both groups is probably related to loss of placental source. The lack of correlation between ADH and B-E levels suggests that the anterior and posterior hypophyses function independently of each other in the postoperative period. In summary, Duramorph administration does not cause a significant release of ADH or B-E but it does prevent the significant rise in B-E that occurs following delivery.

Table Group		T	ime (h	ours)			
0.5		2	4	6	:	24	
	ADH as	perc	entage	of base	eline		
92 (7)		100 24)	109 (22)	130 (30)		203 53)	
Group		,		e (Hours		•	
0.5	2	4	0.5	2	4	24	
	AD	H as	percen	tage of	base]	line	
			229 (146)	111 (25)	168 (85)	85 (22)	
Osmolarity mosm/L							
284 (3)	280 (2)		272 (2)		288 (8)	268 (5)	

ADH values did not differ from the baseline values in both groups (ANOVA).



* - different from the baseline

TITLE: EPIDURAL ANESTHESIA IN DIABETIC OBSTETRICAL PATIENTS

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Introduction. Previous studies (1-3) have described the effects of regional anesthesia on the acid-base status of infants born of diabetic mothers. These studies used excessive glucose infusion before delivery and/or failed to report glucose (G) or other indices of aerobic and anaerobic G metabolism such as lactate (L), pyruvate (P), L/P ratio and excess lactate (XL). Our study reports these indices in diabetic patients undergoing cesarean section (CS) under lumbar epidural anesthesia (LEA) with 2% lidocaine.

Methods. The study was approved by the local review board and patients gave informed consent. The study group included 10 healthy and 10 diabetic patients; Two patients had Class B diabetes, two Class C, three Class R and three Class F. Diabetic patients received regular and NPH insulin until the night before surgery. On the morning of surgery, patients were given an insulin infusion at 1 U/hour with glucose 5G/hour. Blood G levels were measured with a portable glucometer (Chemstrip) and the infusion adjusted to maintain a blood G level of <120 mg/dL. Blood sugar levels > 150 mg% was treated with 2 U of i.v. insulin bolus. Ringers lactate 1500 ml was used for prehydration before LEA. The following were measured at delivery 1): Blood gas tensions and pH in maternal artery (MA), umbilical vein (UV) and artery (UA), 2) D-glucose, L, and P (Spectrophotometric enzyme assay). XL, an index of anaerobic metabolism and base excess (BE) were calculated. Results were expressed as mean + SE and analyzed using ttest.

Results. The maternal glucometer value was $\overline{20\$}$ lower than the value obtained by the direct enzymatic method. One patient from each group required 5 mg ephedrine for hypotension. Apgar scores were similar in the two groups. Blood G in MV, UV and UA in the diabetic group were significantly higher than the corresponding value in the normal group. No other significant differences were noted between the two groups in any of the other indices of anaerobic metabolism. Four neonates from the diabetic group developed hypoglycemia (G < 20mg%) in the postpartum period.

<u>Discussion.</u> Data show that epidural anesthesia is not associated with lactic acidosis in infants born of well-controlled diabetic mothers. The absence of significant difference in the UV L or P in the two groups of patients suggests a normal placental processing of the glucose substrate in diabetic pregnancies. The high

UV G is probably caused by the failure of maternal insulin therapy to affect fetal G levels acutely. The high UV G level at birth may also explain the high incidence of neonatal hypoglycemia.

Table 1:	1: Glucose metabolism					
		Materr	al Vei	<u>n</u>		
	G	L	P	L/P	XL	
Normal	104 (4)	1.48 (0.1)	0.1 (0.01)	17 (1)	0.5 (0.1)	
Diabetes	132 [*] (10)	1.59	0.07	32	0.9 (0.3)	
		Umbilio	al Vei	1		
Normal	88 (3)	1.45 (0.1)	0.08		0.7	
Diabetes	143* (10)	1.2	0.07	20	(0.1) 0.5 (0.15)	
		Umbilio	al Arte	ery		
Normal	77	1.53		21	0.7	
Diabetes	(3) 97* (10)	(0.1) 1.2 (0.2)	(0.03 0.06 (0.03	32	(0.1) 0.6 (0.17)	
Table 2:	: Blood Gases					
		Materna	l Arte	<u>cy</u>		
	PO ₂	PCO ₂	e I	ЭН	BE	
Normal	238	29		42	- 6	
Diabetes	(7) 230	(1) 29	7	(0.1) 7.44	(0.3) -5	
	(7)	(1)		(0.1)	(0.3)	
		Umbilic	al Vein			
Normal	32 (1)	40		7.35	-	
Diabetes	29	(2) 43		7.36	(0.3) -1	
	(2.3)	(2)		(0.01) (0.4)	
		Umbilica	l Arte	<u> </u>		
Normal	20	48		7.3	-3	
Diabetes	(1) 21	(1) 50		(0.01) 7.32	(0.3) -1	
Glucose i	(3)	(3.5))) 	0.02) (0.6)	
*-Signifi	cantly	differen	ப, நம் it from	norma	шшот/ь; l.	
Poferonges						

References.

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 Datta S et al: Anesth Analg 1982;61:662

Title: EPIDURAL VS GENERAL ANESTHESIA IN FETAL DISTRESS WITH VARIOUS ABNORMAL FETAL HEART RATE PATTERNS

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Fetal distress is one of the common indications for emergency cesarean section (CS). In a recent study, Marx et al have shown that regional anesthesia can be safely used for emergency CS for fetal distress. The purpose of this report is to compare the neonatal outcome following emergency CS under epidural (EPID) vs general (GA) anesthesia in various types of abnormal fetal heartrate (FHR) patterns clinically considered as fetal distress.

Methods - Emergency CS for fetal distress was performed in 443 patients from January 1984 - July 1986. GA was administered in 322 patients and EPID in 121 patients. The umbilical venous pH (UV pH) values were available in all patients and both scalp pH and UV pH were obtained in 101 patients. The charts of these 101 patients were reviewed and grouped according to the FHR patterns; Group I (n=46) severe persistent bradycardia with FHR 4 90 lasting for 10 min. or more. Group II (n=27) persistent late decelerations. Group III (n=21) severe repetitive variable decelerations with FHR 470 lasting for more than 90 seconds. Group IV (n=7) - loss of beat-to-beat variability. 67 patients received GA and 34 received EPID anesthesia in this group. Patients who received EPID had epidural catheters already in place for labor analgesia. For emergency CS, the extension of EPID was begun in the labor room with 20-26 ml of 3% 2-chloroprocaine while the patients were being rapidly hydrated with Lactated Ringer's solution. Left uterine displacement was maintained and all mothers breathed oxygen through face masks. In the GA group, anesthesia was induced with penothal 4 mg/kg and succinylcholine 1 mg/kg. Endotracheal intubation was performed. Cricoid pressure was maintained until the correct placement of the tracheal tube was verified by auscultation of the lungs and by end-tidal ${\rm CO}_{2}$ monitoring. The ID and UD intervals, skin incision to delivery interval (SD interval) Apgar scores, UV pH and blood gases and the number of neonatal ICU admissions were noted. The incidence of maternal complications due to rapid extension of the EPID such as hypotension, intravascular injection, total spinal anesthesia due to inadvertant subarchnoid injection, inadequate block, and post operative maternal complications were noted. Statistical analysis was performed by 't' test ANOVA and Chi-square analysis.

Results - In the four groups in whom both scalp pH and UV pH were available, there were no significant differences in the Apgar scores, scalp pH, UV pH, blood gases, NICU admissions, UD intervals and SD intervals. The ID intervals were significantly prolonged in the EPID groups (p<0.01) (see tables) as the induction was begun in the labor room as soon as the decision to perform CS was made. The mean UV pH values were significantly higher than the respective mean scalp pH values (p<0.01, p<0.03) (see tables) in all groups irrespective of the anesthetic technique and the abnormal FHR patterns. However, 97% of babies in the EPID group compared to 79% in the GA group had

higher UV pH than the respective scalp pH values. There were no significant differences in the incidence of hypotension, blood loss or the total amount of fluids administered during the procedures between EPID and GA groups. No major complications related to epidural anesthesia such as unintentional intravascular or subarchnoid injection of local anesthetics occurred in any of the patients in the EPID group. Minor complications such as backache and soreness at the site of epidural insertion were present in six patients in the post operative period.

Conclusions - For emergency CS for fetal distress, in those parturients in whom epidural catheters are already in place for labor analgesia, rapid extension of the epidural anesthesia does not adversely affect the neonatal outcome regardless of the type of abnormal fetal heart rate pattern.

 $\underline{\text{Tables 1}}$ and $\underline{\text{2}}$ - Comparison of scalp pH, UV pH, ID intervals and Apgar scores between EPID and GA groups.

Table 1

	Group (Bradycar		Group II (Late deceleration)		
	EPID (n=17)	GA (n=29)	EPID (r.=10)	GA (n=17)	
Scalp pH	7.19 <u>+</u> 0.07	7.16 <u>+</u> 0.13	7.2 <u>+</u> 0.06	7.17 ± 0.09	
UV pH	7.26 <u>+</u> 0.06*	7.21 ± 0.13*	7.27 <u>+</u> 0.03**	7.22 <u>+</u> 0.1*	
ID interval (min.)	12.4 <u>+</u> 38*	6.0 <u>+</u> 2.6	16.0 ± 3.1*	54 <u>+</u> 3.02	
Apgar 1	7.3 <u>+</u> 21	6.0 <u>+</u> 2.7	7.0 ± 2.7	4.9 <u>+</u> 2.8	
Apgar 5	8.5 <u>+</u> 0.8	8.1 ± 1.4	8.4 ± 0.7	6.9 <u>+</u> 2.8	
*p<0.01 **p<0.03					

Table 2

	Group I (Severe Var		Group IV (Loss of beat-to-beat variabilit		
	EPID (n=9)	GA (n=12)	EPID (n=2	GA (n=5)	
Scalp pH	7.19 <u>+</u> 0.03	7.17 ± 0.05	7.21 ± 0.02	7.09 <u>+</u> 0.09	
UV pH	7.26 ± 0.1**	7.26 <u>+</u> 0.06*	7.33 ± 0.01**	7.20 ± 0.08*	
ID Interval (min.)	10.4 ± 3.1*	6.4 ± 1.1	11.0 ± 2.0*	5.5 ± 2.3	
Apgar 1	7.0 <u>+</u> 2.4	5.5 ± 3.1	8.9 <u>+</u> 1.5	3.0 ± 3.5	
Apgar 5	8.2 ± 0.7	8.0 ± 1.5	9.0 <u>+</u> 0.07	5.5 ± 3.3	
*p<0.01 **p<0.05					

<u>References</u> - Marx GP, Luykx Wm, Cohens: Fetalneonatal status following cesarean section for fetal distress. Br. J. Anaesth 1984, 56: 1009-13.

THE USE OF LABETALOL FOR ATTENUATION OF HYPERTENSIVE RESPONSE TO ENDOTRACHEAL INTUBATION IN

PREECLAMPSIA

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Introduction - Labetalol is an antihypertensive agent possessing a selective post synaptic alpha and non-selective beta adrenoceptor blocking actions. In addition, it has an intrinsic beta, receptor agonistic activity. A recent study using radio-active indium clearance has shown that in preeclamptic women labetalol reduces maternal blood pressure without diminishing the uteroplacental blood flow. I The purpose of this study was to investigate the effectiveness of labetalol in attenuating the mean arterial pressure (MAP) and heart rate (HR) increases following laryngoscopy and intubation in preeclamptic women during cesarean section (CS).

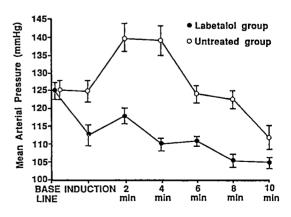
Methods - The study group consisted of 20 preeclamptic women scheduled to undergo under general anesthesia. The study was approved by the Review Board and informed consent was obtained from each patient. The patients were randomly assigned to either the labetalol pre-treatment group or the control group who did not receive any prophylactic antihypertensive therapy. All patients received 6 g magnesium sulfate as a loading dose followed by an infusion of 1-2 g/hr. The blood pressure was monitored every minute using an automatic blood pressure cuff (Dinamap). In addition, the ECG, end-tidal ${\rm CO}_2$ and ${\rm O}_2$ saturation were continuously monitored. Following preoxygention, anesthesia was induced with pentothal 4 mg/kg and succinylcholine 1 mg/kg and endotracheal intubation was performed. Cricoid pressure was applied from the start of induction and maintained until the correct placement of the endotracheal tube was verified by auscultation of the lungs and end-tidal CO, monitoring. Anesthesia was maintained using $N_20-\tilde{0}_2$ (50:50) mixture and 0.5% isoflurane until the delivery of the baby. In the labetalol group, before induction of anesthesia, 20 mg of labetalol was administered intravenously as a bolus followed by 10 mg increments every 2 min. to either lower the diastolic blood pressure below 100 torr or the MAP by 20% from baseline values. A maximum total dose of 1 mg/kg over 10 min. period was not exceeded in any patient irrespective of the decrease in the MAP or diastolic BP. The MAP and HR were recorded before (baseline) and after pretreatment (Induction) with labetalol and at 2, 4, 6, 8 and 10 min. after endotracheal intubation. Similar measurements were made in the control group. At delivery, the Apgar scores, umbilical arterial and venous pH and blood gas values, induction-delivery intervals, uterine incision delivery intervals, blood loss and total amount of fluids administered were noted. The data were analysed by student's 't' test and ANOVA and p<0.05 was considered statistically significant. All values are expressed as mean + SEM.

Results - The patients in the two groups were similar in age, height, weight, parity and gestational age. The baseline MAP and HR were similar in the two groups. Labetalol significantly lowered the MAP from 125 ± 1.6 (SEM) to 112.4 ± 2.2 torr before induction (p<0.001) and the HR from 116.4 ± 2.3 to 96.4 ± 2.3 (p<0.001). After intubation, the MAP

increased significantly in both groups. In the labetalol group this maximum increase in MAP at 2 min. after intubation was 118.4 + 2.3 torr (p₄0.05) whereas in the control group the MAP increased from 126.9 ± 3.09 to 140.5 ± 4.0 torr (p<0.0001) after intubation (See Fig. 1). The difference in the maximum increase in MAP between the two groups was significant, (p<0.0001) (Fig. 1). The maternal HR also increased after intubation in both groups. the labetalol group the HR increased from 96.4 + 2.3 to 101.6 + 2.4 which was not significant whereas in the control group there was significant increase in the HR from a baseline value of 106.8 ± 3.7 to 126.8 ± 5.2 (p<0.0001) after intubation. Ten minutes after intubation, the MAP and HR were still significantly higher (p.0.006 & p.0.0001) in the control group compared to labetalol group. The Apgar scores, umbilical arterial and venous pH and blood gases were similar in the two groups. There was no hypotension, bradycardia or hypoglycemia in the neonates in the labetalol treatment group and none of the babies required special care.

<u>Discussion/Conclusion</u> - The results indicate that in this group of preeclamptic women, pretreatment with labetalol caused significant attenuation of hypertensive response and tachycardia associated with laryngoscopy and intubation. No adverse maternal or neonatal effects were noted.

 $\underline{\text{Fig. 1}}$ - Changes in the MAP in the labetalol treatment group and control group (mean + SEM)



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ATTENUATION OF PSYCHOLOGICAL EFFECTS OF KETAMINE ANESTHESIA BY MIDAZOLAM: A DOSE-RESPONSE STUDY

Authors:

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Introduction. Adverse psychological effects associated with ketamine anesthesia continue to restrict its use and wider acceptance. Midazolam, a water soluble, short acting benzodiazepine, has been shown to be effective in reducing the incidence of these psychologic effects of intravenous ketamine (1. The current investigation was undertaken to study the effect of varying the dose of midazolam on the incidence of adverse psychological reactions of ketamine anesthesia.

Patients & Methods. The study was approved by the ethical committee of the hospital and informed consent was obtained from the patients. One hundred and twenty unpremedicated healthy women (ASA physical status I or II, ages 25-58 yrs) undergoing minor gynaecologic surgery under general anesthesia were included in the study. Patients with hypertensive, coronary artery or cerebrovascular disease, those on concurrent drug therapy or with a history of psychiatric disorders were excluded. The patients were randomly allocated to one of four groups. Group I received 50 mcg/kg, group II 75 mcg/kg, group III 100 mcg/kg and group IV 125 mcg/kg of midazolam intravenously via an indwelling cannula placed in a superficial vein on the dorsum of the hand. Three minutes after the administration of midazolam general anesthesia was induced with intravenous ketamine (2 mg/kg) and maintained with 66% nitrous oxide in oxygen administered using a semi-closed, non-rebreathing Mapleson A circuit. Spontaneous respiration was maintained throughout and increments of ketamine (10 mg) were given intravenously during the procedure as judged necessary by the anesthesiologist. Vital signs were monitored throughout the procedure. Postoperatively vital signs and the incidence of various psychomotor phenomena were recorded by experienced recovery staff who were not aware of the dose of midazolam used. Six to eight hours later a psychological assessment of the patients was performed by one of the investigators who was unaware of the dose of midazolam used. For the purpose of this study any psychological experience which was identified as having occurred during the time when the patient was asleep was classed as a dream. Other psychological phenomena which the patients experienced during or after recovery were carefully recorded. The following definitions were used for evaluation and classification of the patients psychological experiences: i) Perceptive disorders:

a) Hallucination: a disorder involving either visual, auditory or tactile senses and characterised by sensory perceptions in the absence of an external stimulus.

b) Delirium: presence of disorientation, increased arousal, restlessness and agitation accompanied by visual or tactile hallucinations.

c) Confusion: disorientation in time, space or person.

ii) Affective disorders:

- a) Depression: an expression of sadness, grief, sorrow, dejection or misery.
- b) Anxiety: a reaction characterised by a feeling

of excessive subjective apprehension.
c) Fear: similar to (b) but with a recognisable source of danger.

Parametric and non-parametric data were analysed for statistical significance using ancva and chi-square tests respectively. Results were considered significant at P < 0.05.

Resu⁻ts. The four groups in the study were comparable in terms of age and weight (Table 1). There was no statistically significant difference between the groups in the incidence of affective disorders, induction dose, the total dose of ketamine received and the duration of anesthesia (Tables 1 and 2). incidence of perceptive disorders was significantly lower in group IV when compared with the other three groups (Table 2). None of the patients in group IV experienced hallucinations or delirium. Only one patient in this group experienced dreaming.

Discussion. This study suggests that midazolam 125 mcg/kg administered intravenously three minutes prior to induction of anesthesia with ketamine may be useful in significantly decreasing the incidence of perceptive disorders in patients who are at risk of developing these adverse effects.

Reference.

Cartwright PD and Pingel SM. Midazolam and diazepam in ketamine anaesthesia. Anaesthesia 1984; 39:439.

TABLE 1 (mean ±)	SD) Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
Age (years)	25.3 (9.2)	26.3 (10.6)	27.1 (8.4)	31.4 (10.4)
Weight (kg)	58.4 (8.7)	59.2 (10.3)	62.0 (13.5)	62.1 (13.9)
Ketamine	116.8	118.3	124.0	124.0
(induction dose, mg)	(16.9)	(20.5)	(26.5)	(28.0)
Ketamine	167.2	158.7	164.3	153.0
(total dose, mg)	(31.8)	(32.8)	(29.8)	(48.7)
Duration of Anesthesia	a 7 . 9	7.4	7.4	7.5
(minutes)	(2.4)	(2.3)	(2.3)	(2.6)

TABLE 2 Number of patients with incidence of adverse

psyc	chological et	tects.		
	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
PERCEPTIVE DISORDERS Dreams Hallucination Delirium Confusion	18 (60.0%) 6 (20%) 4 (13.3%) 2 (6.7%) 6 (20%)	13 (43.3%) 4 (13.3%) 2 (6.7%) 5 (16.7%) 2 (6.7%)	14 (46.7%) 7 (23.3%) 1 (3.3%) 1 (3.3%) 5 (16.7%)	4 (13.3%)* 1 (3.3%) 0 (0%) 0 (0%) 3 (10%)
AFFECTIVE DISORDEFS Anxiety Depression Fear	9 (30%) 6 (20%) 2 (6.7%) 1 (3.3%)	7 (23.3%) 3 (10%) 2 (6.7%) 2 (6.7%)	9 (30%) 3 (10%) 5 (16.7%) 1 (3.3%)	10 (33.3%) 4 (13.3%) 3 (10.) 3 (10%)

Differed significantly from groups I, II & III (p = 0.0025)

TITLE:

COMPARISON OF THE EEG EFFECTS OF 1653, ISOFLURANE AND ENFLURANE IN PIGS

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JH Donegan MD, PhD, M Cahalan MD

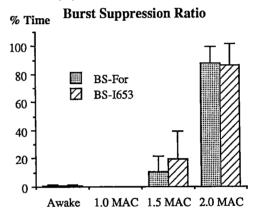
AFFILIATION: Department of Anesthesia, University of California, San Francisco, CA

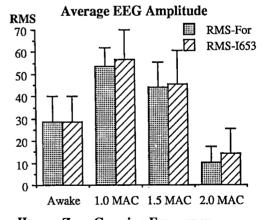
Introduction I653 (CF₂H-O-CFH-CF₃) is a new volatile anesthetic structurally similar to isoflurane and enflurane. Because enflurane has the potential to cause convulsions whereas isoflurane does not, we compared the electroencephalographic activity during anesthesia with I653, isoflurane and enflurane.

Methods Five juvenile female domestic swine were studied after approval of the experimental protocol by the University of California Committee on Animal Research. The average weight was 16 kg. Fasted animals (H₂O allowed ad libitum) were acclimatized to restraint in a padded sling for at least 30 min. Five platinum needles were placed in the scalp to obtain the EEG signals. When the animal appeared relaxed, baseline recordings were made of two channels of EEG. EEG data was digitized by a CerebrotracTM spectral analyzer and transferred to a Macintosh™ computer for quantitative analysis. Each animal was studied with both I653 and isoflurane (sequence prospectively randomized) in separate trials at least 3 days apart. Enflurane was given to two animals on separate occasions. Anesthesia was induced with the agent to be studied. Laryngoscopy and tracheal intubation were facilitated with succinylcholine 2.0 mg/kg iv. Mechanical ventilation was initiated with a tidal volume of 20 cc/kg and ventilatory rate adjusted to maintain normocarbia. Normothermia was maintained. Three concentrations of agent (approximately 1, 1.5, and 2 MAC) were administered in random sequence. Following stable end tidal concentration for 15 min, 4-5 min of EEG were digitized and recorded. The EEG response, if any, to 50 loud hand claps at one s intervals was also recorded. At 1.5MAC, the effects of hypocapnea on CNS activity was assessed by decreasing the P_{BT}CO₂ to 20-25 mmHg. Quantitative EEG parameters were collected and averaged for 1 min intervals at each dose and compared with Analysis of Variance.

Results 1653 and isoflurane produced quantitative EEG values which were statistically indistingishable from each other at equipotent MAC concentrations. Burst Suppression Ratio (Percentage of time per 4 s epoch spent in suppression where suppression was defined as an interval the EEG was $\leq 5.0 \mu$ Volts for at least 240 ms)began to increase just below 1.5 MAC with both agents and isoelectricity was nearly complete at 2.0 MAC (Figure 1a). The Root Mean Square amplitude (RMS or Average EEG Amplitude) peaked at 1.0 MAC and declined with increasing concentrations of both agents (Figure 1b). As predicted by the anatomy of the porcine skull, the occipital amplitudes were about one half the amplitudes from the frontal lead. The Zero Crossing Frequency (the rate at rate the voltage crossed zero) declined with increasing concentrations of either agent from an awake baseline (Figure 1c). In the range between awake and 1.5 MAC of either agents, the Median Power Frequency(MPF), Spectral Edge Frequency(SEF), and NinetyFifth Percentile (F95) all declined with increasing doses. Spectral parameters (MPF, SEF,F95) did not perform well during periods of extensive burst suppression because they continued to track the frequency content of the burst activity, ignoring the predominant quiescent periods. The Theta Ratio parameter decreased at 1.0 MAC to about one half its awake baseline, and thereafter rose with increasing concentration. The relative contribution of alpha and beta power (rA) did not change significantly with changing concentrations of either agent. EEG parameters during hypocapnea at 1.5 MAC were not statistically different than during normocapnea, although there was a suggestion of an increase in SEF and rA during hypocapnea. Auditory stimuli were never noted to induce either epileptiform activity or gross motor seizures during anesthesia with I653 or isoflurane. Both animals exposed to 3.2% enflurane seized during hyperventilation.

<u>Discussion</u> The depression of the EEG produced by I653 appears to closely match the depression seen with equipotent concentrations of isoflurane. With isoflurane, this suppression of EEG activity is associated with a substantial decrease in metabolic requirements of the brain and a possible cerebroprotective effect. One may anticipate similar findings with I653. Finally, the low blood solubility of I653, combined with a clear marker of anesthetic effect in the dose range of clinical interest (burst suppression ratio), make I653 an attractive agent for an automated, closed loop anesthetic delivery system.





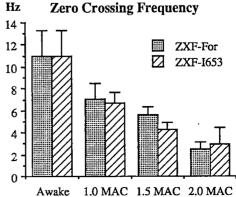


Figure 1 a,b,c. Dose Response of the EEG to I653 or isoflurane. Error bars represent standard deviations

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Title:

DO TRENDELENBURG AND PASSIVE LEG RAISING IMPROVE CARDIAC PERFORMANCE?

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Introduction
been taught that the Trendelenburg position (TP)
and the passive leg raising position (PLR) increase
venous return and augment cardiac output. However,
previous studies of the effects of TP and PLR on
cardiac performance are controversial. TP and
PLR are not necessarily benign. TP reduces
pulmonary compliance, increases intracranial
pressure and increases the risk of passive
regurgitation of gastric contents. In order to
justify the use of TP and FLR, it is necessary to
document that they are efficacious. Therefore, we
studied the effects of TP and PLR on cardiac
performance.

Methods Eighteen patients with coronary artery disease were studied. The study was approved by the institutional research administration committee and all patients gave written informed consent. No patient had valvular dysfunction. A radial arterial catheter and a rapid-response thermistor pulmonary arterial catheter were placed. Patients were anesthetized with fentany1 50-75 mcg/kg, pancuronium 0.1 mg/kg, and oxygen 1007 After endotracheal intubation, a Diasonics (R) 3.5 MHz 2-D transesophageal echocardiography (TEE) probe was introduced. The probe was positioned to obtain a short-axis view of the left ventricle at the level of the mid-papillary muscles with a maximal circular shape. The patients were studied at 3 points in a random sequence: level-supine, 3 minutes of 60 degrees PLR, and at 3 minutes of 20 legrees TP. At each study point, the TEE probe was repositioned to obtain the equivalent short-axis riew, and the transducers were adjusted to the level of the right atrium. Cardiac outputs (CO) and right ventricular ejection fraction (RVEF), and-systolic volume (RVESV), and end-diastolic rolume (RVEDV) were determined by thermodilution technique and an REF-1 American Edwards computer. These measurements were taken in triplicate and averaged. Arterial and mixed venous plood samples were obtained at each study point in order to calculate Q /Q. The TEE images were analyzed using a dedicated Diasonics (R) computer. A single blinded observer traced 4 consecutive left rentricular end-diastolic area (LVEDA) and endsystolic area (LVESA) tracings on an activated grid system. Significance was tested by repeatedmeasures ANOVA. Significance was defined as → **<** 0.05.

Results TP caused significant decreases in HR (5.8%) and RVEF (9%), and significant increases in MAP (5.7%), PAP (17.3%), PCWP (16.5%), CO (7%),

RVESV (22.5%), RVEDV (16.6%) and Q /Q (12.5%). CVP, LVEDA, LVESA, and LVEF did not change. PLR resulted in significant decreases in HR (7.5%) and RVEF (15%), and significant increases in MAP (6.8%), PAP (18.6%), PCWP (20.4%), RVESV (21.7%), RVEDV (13.3%) and Q /Q (18.8%). CVP, CO, LVEDA, LVESA and LVEF did not change. Pertinent data are summarized in the table.

Discussion Previous studies on the effects of TP and PLR have not yielded consistent evidence of improved cardiac performance. In our study we have demonstrated that TP causes only a slight increase in MAP and CO, and that PLR only raises MAP without an increase in C.O. Despite these beneficial effects, there is a considerable cost associated with TP and PLR. The elevations in RVESV, RVEDV, and PAP and the drop in RVEF suggest that PLR and TP tax the right ventricle. Additionally, as demonstrated by the increase in Q /Q, pulmonary function deteriorates in both PLR and TP. Thus it appears that though TP and PLR very slightly improve cardiac performance, in patients with pulmonary disease and/or right ventricular compromise these maneuvers should be undertaken with caution.

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Table	Means ± S	n = 18	* p < 0.05
	LEVEL	PLR	TP
HR	62±9	5 7±9 *	58 ±9
MAP	77±11	83±12*	82±11*
PAP	16±4	19±5*	19±6*
PCWP	11±4	14±5*	13±5
CO	4.24±1.4	4.26±1.3	4.53±1.7*
RVESV	79±37	116±44*	105±37*
RVEDV	149±44	191±50*	183±40*
RVEF(%)	48±11	40±9*	43±10*
Q _s /Q _t	D.16±0.06	0.19±0.06*	0.18±0.06*

Title: THE EFFECT OF VERAPAMIL ON POST-ISCHEMIC RABBIT RENAL FUNCTION DURING FENTANYL ANESTHESIA

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Introduction. There is considerable debate concerning the protective effect of verapamil on the physiologic and metabolic function of post-ischemic kidneys (1,2). Much of the difference may center around the various models of ischemia and the anesthetic drugs used during the experiments. induce renal ischemia, we have cross-clamped the renal arteries and veins of anesthetized rabbits. We have then investigated the effects of verapamil pre-treatment on post-ischemic renal function.

 $\underline{\text{Methods}}.$ Rabbits (3-4 kg) were anesthetized with ketamine (40 mg/kg) IM. After an intravenous catheter was placed, a tracheostomy was performed with 1% lidocaine local anesthesia. The animal was ventilated with 100% oxygen utilizing a Harvard small animal ventilator to maintain normocarbia. Normal saline was administered at a constant rate of 50 ml/kg/hr. Anesthesia was maintained with fentanyl (70 ug/kg) and vecuronium (0.5 mg/kg). A left femoral arterial line was placed by cutdown. After laparotomy, the left renal artery and vein, along with the left ureter, were dissected. Five minutes prior to renal artery and vein clamping, heparin (200 U/kg) or heparin and verapamil (0.1 mg/kg) were infused. After thirty minutes of ischemia, the cross-clamp was removed and a one hour period of reperfusion was allowed before function studies were started. During this period, the ureter was cannulated.

Rabbits were divided into three groups: Group I were controls and underwent laparotomy but no ischemia; Group 2 underwent 30 minutes of ischemia with no verapamil pre-treatment; and Group 3 underwent 30 minutes of ischemia with verapamil pre-treatment. Rabbits in each group were then randomly placed in either the physiologic or metabolic subset. The rabbits in the physiologic group were studied for one hour after the equilibration period. Every ten minutes urine was collected and analyzed for creatinine and sodium concentration. Serum creatinine and sodium were also determined. From this data, creatinine clearance and sodium reabsorption were calculated. The kidneys in the metabolic subgroup were analyzed for ATP concentration and for state 3 and state 4 mitochondrial oxygen consumption which was determined using pyruvate and malate as the substrates for exidation.

Results are reported as mean + SEM. Statistical analysis was performed using the paired t-test and significance was noted for p < 0.05.

Results. Table 1 shows the physiologic function of control kidneys, and kidneys subjected to 30 minutes of ischemia, with and without verapamil pre-treatment. The decrease in creatinine clearance and sodium reabsorption in ischemic kidneys as compared to controls is consistent with previous work. The creatinine clearance and sodium reabsorption in the verapamil treated kidneys were statistically lower than the non-treated ischemic

The mean arterial pressure was not kidnevs. different between any of the groups.

State 3 respiration was reduced in the ischemic kidneys as compared to controls. With the addition of verapamil, state 3 respiration was further reduced. The respiratory control ratios were not decreased in the verapamil treated kidneys because of the concomitant decrease in state 4 respiration.

The concentration of ATP was decreased about 40% from control levels in ischemic kidneys. This decrease, however, was not seen in the presence of

Discussion. In this set of experiments, we have attempted to duplicate the anesthetic technique often used in humans during emergency surgery when renal cross-clamping may occur. In our study, verapamil was not protective of post-ischemic renal function, and in fact, further decreased the viability of these organs. The reduced function of the mitochondria suggests a possible mechanism for the decrease in renal function.

Why does our data conflict with that previously published? The protective effect of verapamil, as shown by a number of investigators, may be due to the norepinephrine model that they used to induce renal ischemia. We have used a cross-clamp to render the organs ischemic. Also, the barbiturate anesthetic universally used in other studies may possibly be protective to post-ischemic renal function.

In summary, our study indicates that verapamil does not provide protection of post-ischemic renal function in a model in which ischemia is induced by cross-clamping.

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	Control	30 min Isch	30 min Isch + Ver
Creat Clear (ul/min/g)	564 <u>+</u> 139	384 <u>+</u> 72.0	241 <u>+</u> 47.3*
Na Reabsorp	94.9 <u>+</u> 1.9	67.5 <u>+</u> 10.7	46.9 <u>+</u> 5.3*
Urine Output (ul/min/g)	17.0 <u>+</u> 4.7	106 <u>+</u> 18.3	135 <u>+</u> 30.7
State 3 Resp (nmoles/min/mg)	36.4 <u>+</u> 4.5	22.0 <u>+</u> 3.1	10.3 <u>+</u> .5*
State 4 Resp (nmoles/min/mg)	8.8 <u>+</u> 1.4	5.0 <u>+</u> 1.0	2.7 <u>+</u> .2
RCR	4.4 <u>+</u> .85	4.5 ± .7	3.8 <u>+</u> .4
ATP (nmoles/g wet weig	1.04 ± .06 ht)	0.60 <u>+</u> .08	0.93 <u>+</u> .15

^{*} denotes significance at p < 0.05 different than the 30 minute ischemic group

MORPHINE CONJUGATES AND VENTILATORY DEPRESSION IN THE DOG

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Introduction. The respiratory depressant action co morphine (M) is well documented (1). M is rapidlə conjugated in vivo to the extent that the free base represents only 10-20% of the total plasma concentration of M plus its conjugates at 1h following its administration (2). Morphine-3-glucuronide (M-3-G) represents the major metabolite of M with morphine-6-glucuronide (M-6-G) being present in considerably smaller concentrations (2. Little is known about the ventilatory effects of morphin≥ conjugates. Furthermore, there is limited information regarding the blood-brain barrier penetration of M-3-G and M-6-G (3). This is an important consideration since it is generally accepted that M acts at intracerebral (principally brain stem) sites to produce ventilatory depression (1). In the present study, using an awake dog preparation and a 4h IV infusion of M-sulfate (MS), we evaluated the time-related distribution between plasma and CSF of M base and M-3-G and their effects on ventilatory drive and PaCO2. In addition, we studied the same effects on ventilation of fourth ventricular administration of M-3-G.

Methods. Mongrel dogs (25-30 kg) were surgically prepared with chronic indwelling femoral arterial and venous catheters, guide cannulae for insertion of spinal needles into the 4th ventricle and cisterna magna, and tracheostomy. Eight to 14 days were allowed for surgical recovery. Two experimental series were employed. In both, the dogs were conscious but restrained in a stanchion. In the first, MS was IV inflused at a constant rate (10 ug/kg/min) following a loading dose of 1 mg/kg. [140] morphine was included in the infusate. Arterial PaCO₂, PaO₂, plasma ¹ C activity and plasma morphine base levels (via HPLC). Cisternal CSF samples were taken every 30 min for analysis of ¹⁴C activity and morphine base. Ventilatory drive evaluations were performed every asses. Ventilatory drive evaluations were performed every 30 min using a modification of a CO₂ rebreathing method. Assessments were based on PaCO₂ vs 1 seconspiratory occlusion pressure change (dp/dt in mmHg/sec). Among animal comparisons were facilitated using the dp/dt value at PaCO₂=70 mmHg during rebreathing. In the second series, M-3-G was prepared in the partificial CSE callition and different writers. an artificial CSF solution and delivered using a 4th ventricle to disterna magna perfusion (VCP) system. CSF composition and conditions for study have been described elsewhere (4). All drug perfusions (at 0.4 ml/min) were preceded by a 2 h period of VCP with drug-free CSF (control). We then evaluated the effects on ventilatory drive and PaCO2 of VCP with M-3-G at 1, 10 and 50 ug/mL

Results. In the IV MS infusion series the disternal CSF/plasma ratio of M base remained relatively constant while the disternal CSF/plasma ratio of total M (based on $[^{14}\mathrm{C}]$ morphine specific activity) was found to rise from 0.069 at 1 h to 0.13 at 4 h. Over the same period, PaCO₅ gradually increased, and ventilatory drive (dp/dt_{7C}) gradually decreased. Perfusion with M-3-G at 1 ug/ml resulted in a slight depression of ventilation (increase) PacO2) but no change in ventilatory drive. During VC? delivery of M-3-G at 10 ug/ml, ventilatory drive increased to 143% control but PaCO2 remained unchanged. Perfusion with M-3-G at 5C ug/ml resulted in a 1815. increase in ventilatory drive and a decrease in PaCO2.

Discussion. Our observation of a constant CSF/plasma ratio of M base while the CSF/plasma ratio of total M (M base + conjugates) continued to increase during the 4 h MS infusion is probably the result of increasing penetration of M conjugates into the CSF over time. This is consistent with the highly polar nature of M-3-G and M-6-G (3). The possibility exists that the gradually increasing ventilatory depression over time, in the face of a constant disternal CSF M base concentration, is at least partly related to increasing presence of gluouronides in the CSF. However, VCP delivery of M-3-G into the CSF produced ventilatory stimulation, not depression. We have previously shown, using the identical VCP delivery system, that MS causes significant depression of ventilation (4). The ventilatory effects of VCP administered M-6-G is currently under investigation.

Table 1. Intravenous MS infusion studies

	Control	Time of 1h	Infusio 2h	on 3h	4h
PaCO ₂ (mmHg)	38.8	54.0	55.1	59.8	60.9
dp/dt ₇₀ (% control)	100	40.3	34.7	38.7	25.6
morphine base (CSF/plasma rati	- io)	0.48	0.44	0.36	0.42
total morphine	-	0.069	0.082	0.098	0.13

Table 2. VCP glucuronide administration studies.

	Control	M-3 - G	M-3-G	M-3-G
ug/ml	0	1	10	50
PaCO ₂ (mmHg)	38.9	42.7	39.4	35.8
dp/dt ₇₀	100	94.6	143.2	180.7

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HYPERCARBIA DEPRESSES CEREBRAL OXYCEN CONSUMPTION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS A.T. Rogers, MB ChB, D.S. Prough, MD, D.A. Stump, PhD, K.C. Angert, MD, J.F. Butterworth, MD, J. Phipps, RN, L. Hinshelwood, MA, L. Charles, CCP Departments of Anesthesia and Neurology, Wake Forest University Medical Center, Winston-Salem, North Carolina 27103 Title: Authors: Affiliation:

Introduction: Increasing PaCO2 elevates cerebral blood flow (CBF) during hypothermic cardiopulmonary bypass (CFB). Hypercarbia's influence on cerebral oxygen consumption (CMBCO) is controversial. We report CMRO2 changes influence by altering PaCO2 during CFB.

Methods: We studied 26 patients, free of chronic hypertension or cerebrovascular disease, undergoing cardiac surgery. All gave informed consent for entry into a study approved by the Clinical Research Practices Committee. After premedication with lorazepam and morphine, we induced narcosis with fentanyl 75 µg/kg. No other drugs were given until completion of CBF measurements. We placed a retrograde 15 cm, 20 gauge internal jugular vein catheter for sampling of cerebral venous blood.

During hypothermic, nonpulsatile CFB, CBF was measured twice in each patient. In Group I (N=1), was measured twice in each patient. In Group I (N=1), was measured twice in each patient in random order, or an each pat

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Table 1. (Mean ± SD)

		PaCO ₂ (mmHg)	MAP (mmHg)	NPT (°C)	$(\text{L.min}^{\bullet_{-1}}\text{m}^{-2})$	Hct (Vol %)
Group I	A B	36±2 45±2	70±9 70±9	27.3±0.6 27.2±0.7	1.9±0.4 1.9±0.4	23±3 24±3
Group II	A B	55±3 68±2	69±8 68±9	27.6±0.7 27.6±0.9	1.9±0.3 1.9±0.3	26±4 26±4

Table 2. (Mean ± SD)

		(PaCO ₂	(m1.100g CRF .min -1)	CMRQ2 (ml.100g .min ⁻¹)
Group	Ι	A B	36±2 45±2	12.8±5** 15.1±3**	0.38±0.12 0.39±0.15
Group	II	A B	55±3 68±2	25.7±9* 28.7±5*,**	0.31±0.09** 0.21±0.07

**Intergroup difference (P<0.05)
Intragroup difference (P<0.05)

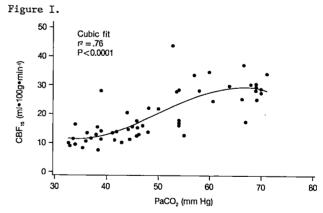
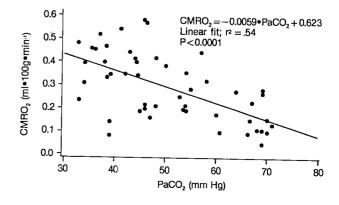


Figure II.



Title: A COMPARISON OF ANESTHETIC INDUCED PLATELET DYSFUNCTION BETWEEN FLUOTHANE, ETHRANE AND ISOFLURANE.

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Introduction. A few studies using isolated inhalational anesthetics have been able to demonstrate that inhalational anesthetics induce platelet dysfunction. The amount of dysfunction has been noted but a comparative study has never been done. The purpose of this study was to compare the degree of platelet dysfunction induced by the three common inhalation agents.

Methods. This project received approval of the institutional human review committee. One hundred eight ASA 1-2 patients who had not been recently exposed to any medications with known platelet effects were entered into our study. The anesthetic agent was randomly assigned, and the groups were approximately equal. No patients were premedicated, and each patient served as their own control. A pair of blood samples was obtained from each patient. The first prior to anesthetic exposure, and the second after 30 minutes cf inhalational anesthesia. All patients were induced with sodium thiopental and had intubation facilitated by succinylcholine. Maintenance anesthesia consisted of 60% Nitrous oxide and 1-2 mac of Halothane, Ethrane or Isoflurane. After obtaining the specimen from the anesthetized patient the airspace above the liquid sample was flushed with 1-2% of the specific inhalation agent which had been clinically used to prevent loss of drug from the plasma. All platelet analysis was performed using the Sonoclot^R analyzer which measures the visceoelastic properties of the forming clot. The shoulder peak interval was usec to qualitatively analyze the platelet function. The samples underwent statistical analysis using the students t-test to determine anesthetic induced platelet dysfunction within the group and anova to determine statistical significance between the groups.

Results. Three patients in the isoflurane group were removed from the statistical analysis as their values post exposure for outlay the rest of the values.

There was a statiscally significant difference between pre-anesthetic platelet function and the post-anesthetic platelet function for each of the three groups (p > 0.01). Using anova there was ac statistically significant difference between the three groups. There was considerably greater difference between Halothane and Ethrane or Isoflurane than between Ethrane, and Isoflurare (see table 1).

<u>Discussion</u>. This study has shown that all three agents can induce platelet dysfunction. It should be noted that the dysfunction though experimentally significant rarely exceeded the normal limits of the analysis. Three women in the Isoflurane group who had normal platelet function prior to exposure developed profound platelet dysfunction after 30 minutes of isoflurane exposure. This platelet dysfunction appeared to be clinically evident during their surgical procedures, and they required intraoperative transfusions.

The mechanism of action of anesthetic induced platelet dysfunction is postulated to be secondary to their potential for increasing cyclic AMP within the patelet. This leads to a decrease level of ADP which is essential for platelet aggregation. We conclude that inhalation agent induced platelet dysfunction is experimentally demonstrable, but rarely becomes clinically significant. Halothane appears to commonly induce a slightly greater amount of dysfunction than ethrane or isoflurane though this was not statistically significant. Caution should be taken in those patients presenting for anesthesia who have taken medications known to alter platelet function because the combination of these drugs with inhalation agents may potentiate anesthetic induced platelet dysfunction.

Table 1

Group	n	Mean difference of shoulder- Peak interval pre & post exposure
Halothane	28	15.4
Ethrane	30	10.7
Isoflurane	5 0	10.8

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O, SAT, HR AND MAP AMONG PATIENTS RECEIVING LOCAL ANESTHESIA: HOW LOW/HIGE DO THEY GO? ER Rothfusz, M.D., DS Kitz, Ph.D., RW Andrews, B.A., SJ Aukburg, M.D., JE Lecky, M.D. Center for Research in Day Surgery, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104

INTRODUCTION: Previous work in our Day Surgery Unit (DSU) suggests that decreases in hemoglobin saturation (SAT) and large swings in heart rate (HR) and mean arterial pressure (MAP) are not rare events among patients receiving local anesthesia (LOC). The purposes of this study were to build an on-line database consisting of health history and intra-operative physiologic data, to identify potentially adverse intraoperative events and to determine the medical history of LOC patients with these events.

METHODS: Database: We used a local area network to record data continuously from the pulse oximeter and automated blood pressure monitor in each operating room (OR). DSU health survey information and OR record data were entered independently. All data are stored in a VAX 8200 supermini computer using a relational database. Pulse oximeter data (SAT, HR) were recorded every minute. MAP was recorded every three minutes. We used this system during a $2\frac{1}{2}$ month period to record SAT, HR, MAP, health survey and OR record data for patients receiving LOC in our DSU. Events: There were no bradycardic or hypotensive events. Thus, we selected lowest SAT, and highest HR and MAP as indicators of potentially adverse intraoperative events. To identify events and to eliminate possible artifact data, we selected SAT and HR values that appeared for at least two contiguous minutes. We determined the frequency with which levels of each parameter occurred. Medical History: We used the relational database to identify each patient's current health status, previous illnesses and current medications. We then used this information to determine each patient's relevant medical history.

RESULTS: Database: SAT, HR, MAP, health survey and OR record data were available for 149 patients. Events: Four of 72 (5.5%) LOC patients had a SAT of 90% or less (Table 1), 12 of 77 (16%) had a HR of 101 or greater and 31 of 149 (21%) had a MAP of at least 121. Medical History: One of the four patients with coronary artery disease (25%) and one of the eight patients with hypertension (13%) had a HR greater than 126 (Table 2). All of the patients with coronary artery disease had MAPs of 121 or greater (Table 3). Six of 14 (43%) patients with hypertension also had MAPs of at least 121.

DISCUSSION: Many patients receive LOC for surgical, dental and radiologic procedures, often in settings where no anesthesia personnel are available. Little is known, however, about the intraoperative physiologic status of these patients and which parameters should be monitored. Our database, which includes health history, OR record and intraoperative automated monitor data, allows us to identify potentially adverse intraoperative events. We found that SATs of 90% or less, HRs of at least 101 and MAPs of at least 121 are not rare events among patients receiving LOC. Moreover, it appears that patients with pre-existing cardiovascular disease and hyper-

tension may be at increased risk for such intraoperative physiologic changes. These preliminary findings suggest that enhanced evaluation and monitoring of LOC patients may be warranted, particularly as the number of less healthy and older patients undergoing outpatient procedures increases. In addition, reimbursement schemes should acknowledge that anesthesia care may be appropriate for certain groups of LOC patients (e.g., those with cardiovascular disease, hypertension) who appear to be at increased risk for adverse intraoperative events. Further development of such a database will allow us to identify more precisely the factors (e.g., age, sex, hypertension, etc.) which predispose patients to abnormal intraoperative physiologic changes.

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Hemodynamic and oxygen saturation changes among
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Table 1: Number of LOC patients by SAT, HR and MAP levels.

		Lowest S	<u>AT</u>	
<u><85%</u>	86-90%	91-95 <u>%</u>	96-100%	Total # Patients 72
1	3	23	45	
		Highest	HR	
<50	<u>51-75</u>	76-100	101-125	$\frac{126}{3}$ 77
0	24	41	9	
		Highest 1	MAP	
<u>61–80</u>	81-100	101-120	$\frac{121-140}{24}$	141+
9	48	61		7 149

Table 2: Number of LOC patients by medical history and highest HR

	Highest HR					
	<u>√50</u>	<u>51-75</u>	<u>76-100</u>	101-125	126+	TOTAL
Ccronary artery disease	0	2	1	0	1	4
Hypertension	0	3	4	0	1	8
Nc relevant disease	_ 0	19	36	9	_1	65
TCTAL	0	24	41	9	3	77

Table 3: Number of LOC patients by medical history and highest MAP

	Mighest MAP					
	61-80	81-100	_01-20	121-140	141+	TOTAL
Ccronary artery disease	0	0	0	1	3	4
Hypertension	1	1	6	3	3	14
No relevant disease	8	47	55	20	1	131
TOTAL	9	48	61	24	7	149

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Title:

FAILURE OF FRESH FROZEN PLASMA TO REDUCE BLOOD LOSS AND BLOOD REPLACEMENT AFTER CARDIOPULMONARY

RYPASS

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Introduction. Despite the recommendations of the 1984 Consensus Conference (1), fresh frozen plasma (FFP) is still being administered prophylactically to offset the dilution of clotting factors after cardiopulmonary bypass (CPB)(2,3). An opportunity to study its efficacy in this setting was provided when a surgical team acutely substituted 5% albumin for FFP in its fluid administration protocol.

The anesthetic and intensive care unit (ICU) records of 100 consecutive patients who had undergone elective aortocoronary bypass grafting by the same surgeon were reviewed; 52 from immediately before the change in protocol (Group F), and 48 from immediately after (Group c).

All patients underwent non-pulsatile CPB with a Shiley S100A bubble oxygenator, crystalloid prime, and moderate hypothermia. During bypass the activated clotting time (ACT) (International Technidyne Hemichron) was maintained > 480 sec. Heparin neutralization with protamine was confirmed by the return of serial ACT's to normal and by the absence of a heparin effect in an automated protamine titration (Hemotec Hepcon). Bank blood was given after bypass when the hematocrit was < .32.

In Group F 2 units of FFP were administered for bleeding prophylaxis and additional units were given for volume replacement. In Group C no FFP was administered. 5% albumin was given for volume replacement.

PT and PTT were determined on arrival in the ICU. Blood loss was defined as the 24 hr chest tube drainage. Statistical comparisons were made using Student's t, Mann-Whitney rank sums, and chi square tests. P values < 0.05 were considered significant.

Results. There were no differences in age, number of grafts, bypass time, male:female ratio, or distribution of anesthesiologists.

On patient in Group F and 2 in Group C required re-exploration for bleeding and were not included in the table. In all 3, specific bleeding sites were found. The 24 hr blood loss was < 1100 ml in all patients except for 2 in Group F whose blood losses were 1700 ml. These 2 patients account for the larger mean blood loss in Group F, although the difference between the 2 groups was not significant. Also the administration of platelets to these 2 patients allowed the differences between groups in the number of units of platelets to achieve significance.

The number of units of blood (whole, packed cells, or both) transfused did not differ between groups. The greater number of donors in Group F was the result of the highly significant difference (P < .001) in the number of units of FFP administered.

Discussion. Prophylactic administration of FFP after CPB did not reduce blood loss, lower the number of patients re-explored, or produce more normal results on coagulation tests. Substitution of 5% albumin for FFP significantly reduced the number of blood components per patient and thereby reduced the risk of disease transmission, sensitization, and untoward reaction.

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Table. Influence of FFP on blood product administration, blood loss, and clotting parameters.

Group	<u>F</u>	<u>c</u>
Components transfused Blood (units) FFP (units) Platelets (units)	5.5 ± .3 5.8 ± .5 2.7 ± .8	5.3 ± .2 0.2 ± .1* 0.9 ± .4**
Donors	14.0 ± 1.2	6.4 <u>+</u> .5*
24 h blood loss (ml)	630 ± 44	550 <u>+</u> 24
PT (sec) PTT (sec)	$14.6 \pm .1$ $31.6 \pm .8$	15.2 ± .1** 29.7 ± .5**

Values represent meam + SEM; *p < .001; **p < .05

EFFECT OF ANESTHETICS ON HYPERTENSIVE RESPONSE TO CEREBELLAR RETRACTION DURING POSTERIOR FOSSA SURGERY

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Introduction: Hypertension, bradycardia, and ectopy can occur during posterior fossa brain surgery. [1] Moderate to severe increases in blood pressure are associated with retraction of the cerebellum during posterior fossa craniectomy and microvascular decompression of the fifth cranial nerve in patients suffering from tic douloureux. This study was performed to determine if anesthetic agents differ in their ability to attenuate this hypertensive response.

Methods: Following approval by the local committee on human research, 29 patients ASA Class II and III gave written, informed consent to participate in this study. One surgeon performed all operations. this study. One surgeon performed all operations. Patients who had an average pre-operative blood pressure (BP) greater than 160/100, or a history of pulmonary, renal, or hepatic disease, or who regularly took narcotics to control pain were excluded. larly took narcotics to control pain were excluded. Premedication was with triazolam, 0.125 mg, po given I hr pre-operatively. Anesthesia was induced with thiopental, 4 mg/kg IV, lidocaine, 1 mg/kg IV, vecuronium, 0.1 mg/kg IV, and 60% nitrous oxide. The trachea was intubated and ventilation controlled to maintain $PaCO_2 = 3O + 3$ (S.D.) mm Hg. Arterial blood pressure zeroed to the dependent external auditory meatus and the electrocardingram external auditory meatus and the electrocardiogram were recorded continuously on a Hewlett-Packard 7402A strip chart recorder. Patients were randomly assigned to one of three anesthetic groups: halothane/ N_20 ; isoflurane/ N_20 ; sufentanil/ N_20 . The anesthetist was instructed to deliver enough anesthetic (pre-cerebellar retraction) to control systolic BP at 10-20% below the average of all ward BP's recorded. End-tidal concentrations of anesthetics were monitored continuously by massspectrometry and recorded. The sufentanil/ N_2O group received sufentanil 2.7 \pm 0.9 mcg/kg IV, in divided doses to attain the desired BP. The BP in two patients receiving sufentanil/N₂0 could not be controlled with sufentanil doses to 6 and 12 mcg/kg, respectively, and the results from these patients were not included in the analysis. Vaso-dilators and beta adrenergic blocking drugs were not administered intra-operatively. The surgeon retracted the cerebellum with a malleable retractor and then fixed it to the skull via a self-retaining apparatus. The largest blood pressure change during this time was noted and compared among groups by analysis of variance (ANOVA). 95% confidence intervals were then used to test for differences among groups. Student's t-test was used to compare MAC equivalents for the two volatile anesthetic groups and ANOVA for other values in the table. P<0.05 was considered significant.

Results. In every patient, BP increased during cerebellar retraction. Halothane/N₂O was more effective in attenuating this response when compared to isoflurane/ N_2O (see table). Sufentanil/ N_2O was intermediate and not statistically different from either the halothane/ N_2O or isoflurane/ N_2O group. However, two patients in the

sufentanil/N2O group had to be removed from the study due to uncontrollable hypertension pre-retraction. Also, 4/7 of the remaining sufentanil/N2O patients required naloxone to restore adequate ventilation at the end of surgery. MAC equivalents for the volatile anesthetic groups were not different. In only one patient (sufentanil/ N_2O) did HR change more than 5 beats/min during the study period (HR 75 to 35). No ectopy was noted in any patient.

<u>Discussion</u>. The mechanisms for the hypertensive response to cerebellar retraction remain unknown. Our results suggest that, of the anesthetics studied, halothane/ N_2O is the most effective in attenuating this response. The mechanism of halothane's effect is also unknown. However, Seagard, et al., [2] have found that, at 1 MAC, halothane depresses baroreceptor reflex changes in sympathetic activity more than isoflurane. Perhaps this mechanism, or a similar one, applies to our results. This study may help anesthetic decision making as follows: (1) In posterior fossa surgery where hemodynamic stability is of primary concern, halothane/N₂O may be preferable to isoflurane/N₂O; (2) in patients where hemodynamic change to brain stem manipulation is desirable as an alert to halt surgical resection, isoflurane/N2O may be preferred.

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isoflurane on the baroreceptor reflex. Anesthesiology 1983; 59:511-520.

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N	<u>Halothane</u> 8	<u>Isoflurane</u> 9	Sufentanil 7
Ages	57 ± 11	62 ± 8	51 ± 13
MAC *	1.05 ± 0.27	0.96 ± 0.17	
Ave Ward BP	136 ± 17 85 ± 13	$\frac{130 \pm 14}{77 \pm 14}$	136 ± 19 80 ± 9
Pre-retract BP	$\frac{117 \pm 9}{73 \pm 14}$	$\frac{104 \pm 11}{60 \pm 7}$	123 ± 15 70 ± 7
Peak increase BP	$\frac{17 \pm 6}{10 \pm 5}$ **	<u>38 ± 20</u> 26 ± 13	26 ± 19 13 ± 10

All values mean \pm S.D.

MAC value does not include contribution from N20

P<0.05 Halothane different from Isoflurane All other comparisons N.S.

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ANALYSIS OF NITROUS OXIDE AS A SOLE ANESTHETIC IN HUMANS IN HYPERBARIC CONDITIONS

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ntroduction: Since 1868 mixtures of nitrous oxide and xygen have been advocated as a means to produce analgesia nd anesthesia for surgery. If nitrous oxide is the sole gent, the concentrations needed (MAC=1.04) to produce dequate anesthesia cannot be utilized outside of a yperbaric chamber without delivery of a hypoxic gas ixture. In 1878, Paul Bert anesthetized a dog in a yperbaric chamber at 1.2 ATA with a mixture of five parts 20 and one part 02.(1) In 1949, Falconer and Pender foduced anesthesia in human volunteers breathing 50% N2 nd 50% 02 at 2 ATA.(2) In 1982, Hornbein, Eger et al eported anesthetizing seven volunteers at 1.55 atm begutte N.O to determine MAC.

bsolute N₂O to determine MAC.
ethods:
With approval from our Clinical Investigation ommittee, eight human volunteers were anesthetized in a yperbaric chamber at 2 ATA with nitrous oxide and oxygen. 11 volunteers were ASA I males age 20-31 years who had een NPO for at least eight hours. Prior to pressurization n 18 gauge IV catheter was inserted with administration of actated Ringers. Monitoring consisted of a precordial tethoscope, EKG, ear oximetry, blood pressure by Dynamapo nd regular sphygnomanometer, axillary temperature and easurement of inspired and expired 0, N20 and CO oncentrations by a Perkin Elmer MGA 1100 mass pectrometer. All resuscitation equipment and medications ere present. Chamber pressure was increased to 2 ATA. nesthesia was induced in each volunteer by inhalation of ital capacity breaths of nitrous oxide 1.5 ATA. Loss of onsciousness was determined by the inability to follow imple commands and loss of eyelid reflexes. After a stable evel of anesthesia with spontaneous ventilation had been stablished and an intravenous precurarizing dose of uccinylcholine (20 mg) was given, followed in three inutes by a paralyzing dose of 1.5 mg/kg. This was ollowed by endotracheal intubation and assisted entilation until return of spontaneous respirations. One f the subjects was not intubated, but anesthesia was aintained by mask for two hours. Six subjects were nesthetized for four hours and one for three hours. The ntubated patients had orogastric tubes connected to uction. There was no regurgitation or vomiting at nduction. Ventilation was spontaneous through a emi-closed circle system. At the end of the anesthetic, 20 was turned off and spontaneous ventilation continued ith 100% 0. Extubation as performed when the subject was wake and capable of adequate airway protection. Chamber ecompression was started when ETN, was \leq 0.06 ATA. A 0-minute decompression stop at a depth of 10 feet was used or those anesthetized for four hours.

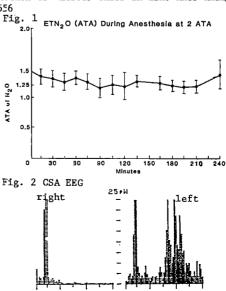
esults: At induction, all subjects lost consciousness in $\stackrel{<}{\sim} 0$ seconds. Inhalation induction was associated with an ncrease in mean arterial pressure (MAP) ranging from 20-47 mHg (mean 36 mmHg), tachypnea (respiratory rate 20-47 reaths per minute) and tachycardia (peak rates 80-140 pm). Peak increases occurred between 3 and 7 minutes of nduction. Changes returned to a lower stable baseline in $\stackrel{<}{\sim} 5$ minutes in all subjects except one in whom 50 minutes are required. During anesthesia ETCO2 ranged from 3.6% to 1.0% during spontaneous respiration. ETN20 was followed closely and adjustments made depending on subject seessment. A relaxed anesthetized state was produced by a arrow range of ETN20 (Fig. 1). During this phase, each ubject had dysconjugate gaze. With ETN20 levels higher han previously assessed MAC, each volunteer responded to aryngeal suction with coughing and tachycardia. Each

volunteer periodically exhibited waves of sympathetic associated with diaphoresis, tachycardia and hypertension. These change occurred without variation in ETN 0 or ETCO. Clonus was demonstrated in all subjects. The limbs involved and the degree varied. Frank opisthotonic posturing was demonstrated by four subjects. The compressed spectral array (Neurotrac) demonstrated elimination of gas wave activity with induction. However, during light levels of anesthesia and high levels of ETN20, increased alpha and beta wave activity was demonstrated, initially in the dominant atmosphere (Fig. 2). At the end of anesthesia each subject followed simple commands within 15 minutes. With high (> 10 L/min) $\hat{0}_2$ flows, the excitement phase during N_2 0 washout was rapidly transited and commands were followed in < 6 minutes. After anesthesia, four subjects had mile nausea only (one with slight dizziness for 20 minutes), two no nausea whatsoever, and two marked nausea and vomiting.

Discussion: N_2O anesthesia can be well maintained at 2 ATA. It is associated with increased sympathetic and motor activity which would make surgery difficult without paralysis. At greater than previous determined MAC values, all subjects responded with movement to laryngeal suction. The anesthetic is rapidly reversible and nausea and vomiting is not a significant problem in the majority. There is no decompression schedule available for N_2O breathing at depth. A 90-minute decompression stop at 10 feet was chosen empirically and has resulted in no associated problems.

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Title: TENS: ARE WE MAKING THE BEST USE OF THIS MODALITY IN CHRONIC PAIN THERAPY?

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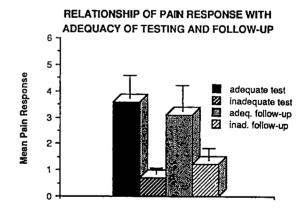
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introduction. The nervous system contains protective mechanisms or control systems to diminish painful experiences, and electrical stimulation of nerve fibers can activate these control systems. A factor that has been of significance in making stimulation treatment practical is the development of transcutaneous electrical nerve stimulators (TENS), which patients can use without any restrictions in their daily lives. Eriksson and Sjolund have pointed out that in a variety of investigations it has been reported that 12-35% of the patients have had a good response to treatment with TENS during a follow-up period of 4-12 months. These authors have pointed out that it is important not only that all forms of stimulation be given an adequate trial, but that the initial placement of the electrodes, information to the patient, and follow-up, be carefully controlled if a successful treatment is to be obtained. Also, because of the complexity of the chronic pain problem a careful selection of the patients who would be suitable for TENS should be carried out prior to the introduction of this modality. In particular patients with major psychosocial operant factors in the maintenance of chronic pain problems have not responded well to this form of therapy. In this study we have analyzed chronic pain patients presenting to a University Pain Clinic, who have been treated for their chronic pain problem with TENS to determine how the technical aspects of the application of TENS, and psychosocial factors, may have a bearing on the response to TENS.

Method. Following approval of the human subjects investigation committee, 31 patients presenting to the University of Michigan Chronic Pain Clinic were asked to complete a detailed questionnaire, including a series of questions relating to depression. In addition, they all completed the Eysenck Personality Inventory. On the day of their scheduled visit to the clinic, the patients were interviewed by a clinic nurse who conducted a structured interview with regard to the use of TENS in the patient's chronic pain problem. patients rated their pain as having no response, poor, moderate, or good. In addition, they were presented with a visual analog scale and asked to mark the degree of pain relief they experienced using this modality, 0 being no response and 10 being complete pain relief. The adequacy of the initial testing of TENS and followup in the relief of chronic pain was based on the criteria outlined by Eriksson and Sjolund and assessed by a different staff member than the person administering the structured interview. At the conclusion of the clinic visit the patient's data was collected and scored. The results were then subjected to statistical analysis.

Results. Of the 31 patients, 11 were male, 20 were female, with an age range from 24-71. Twenty-four of the patients were suffering from low back pain and/or myofascial pain, and 7 patients were given a diagnosis of neuralgia. Eleven of the patients were still using TENS, and 10 of the patients were actively involved in litigation compensation issues. There was no correlation between those still using their TENS and those pursuing active litigation compensation, and there

were no significant differences between the patients using the TENS, those in active litigation compensation, and their depression or personality scores. All of the patients with a diagnosis of neuralgic pain had a poor response to TENS and none of them were still using this mode of therapy. There was a significant correlation between the pain and TENS responses and the adequate testing and follow-up of the pctients. There was no correlation between the Eysenck Personality Inventory scores or depression scores and either the degree of pain relief achieved, or of the response to transcutaneous electrical nerve stimulation. There was a highly significant correlation between the degree of neuroticism as determined by the Eysenck Personality Inventory and the depression score as obtained from the depression rating scale used in the Patient Assessment Narrative. Partial correlation coefficient = 0.84 R-SQR. = 0.70.



<u>Discussion</u>. This study suggests that psychosocial factors operant in these chronic pain patients conditions did not have any bearing on whether or not the patient responded to transcutaneous electrical nerve stimulation. The success achieved using this form of chronic pain therapy was related to the adequacy of testing of these patients at the initial visit, and the adequacy of their follow-up. From the criteria outlined in the method, only 11 out of the 3 patients had adequate testing at the initial visit, and only 8 of these patients were adequately followed up.

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HTLE: EFFECT OF DELIBERATE HYPOTENSION ON ARTERIAL TO PEAK EXPIRED CARBON DIOXIDE TENSION DIFFERENCE

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Introduction. In 1963, Eckenhoff et al found an ncrease in the physiological dead space, up to 75% f the tidal volume during deliberate hypotension. he increase was mainly in the alveolar dead space. In a study of 7 patients, Askrog et al found a small ncrease in the physiological dead space during eliberate hypotension. More recent investigations ave failed to demonstrate increases in the alveolar ead space during deliberate hypotension in the upine position or with slight head-up tilt, in dults or children. The purpose of the present inestigation was to re-evaluate the effect of delibrate hypotension on the alveolar dead space. The rerial to peak expired carbon dioxide partial ressure difference P(a-pe)CO₂ was utilized to ssess the magnitude of change of alveolar dead pace.

<u>Methods.</u> The study was approved by the instituional investigative committee and informed consents ere obtained. Thirty eight patients in whom reuction of blood loss was sought were studied. urgical procedures included: scoliosis correction ith instrumentation in the prone position (13 atients), hip arthroplasty in the supine position 2 patients) and head and neck procedures in a headp tilt (10-25 degrees), (13 patients). A radial rtery was cannulated prior to anesthetic induction or arterial blood pressure measurements and blood as sampling. After induction of anesthesia with hiopental and fentanyl, intubation was facilitated ith a muscle relaxant. Anesthesia was maintained ith either enflurane or isoflurane in oxygen and euromuscular blockade. Ventilation was controlled t constant tidal volume and rate maintaining a aCO, between 30 and 40 mm Hg. After a clinical teady state was achieved, hypotension was gradually nduced with trimethaphancamsylate infusion (0.2% in % dextrose in water). Propranolol was administered n 0.1 mg increments to control increases in heart ate. In patients undergoing surgery of the head nd neck, a head-up tilt (10-25 degrees) was utilzed. Paired arterial blood gas analysis and peak xpired carbon dioxide partial pressure (PpeCO2) alues as measured by a calibrated mass spectrometer ere obtained before induction of hypotension control) and 15, 30,60,90 and 120 minutes during ypotension. In 21 patients, samples were obtained ollowing the return of blood pressure to 90% of he prehypotensive level. Body temperature was aintained between 36.1 and 37.10 throughout the nvestigation. Significant statistical differences rom control were identified with a paired t-test nd statistical significance was accepted when <0.05.

Results. In patients undergoing scoliosis orrection, (mean age = 17.3 years) there were no ignificant changes in $P(a-pe)CO_2$. The mean gradienta s 2.88 mm Hg before hypotension and remained etween 1.6 and 3.3 during hypotension in spite of a eduction in mean arterial pressure to 52.0 mm Hg. n patients undergoing head and neck surgery (mean ge = 45.0 years) there were no significant changes n $P(a-pe)CO_2$ during the first hour of hypotension, ut a slight increase was noted at 90 minutes. In

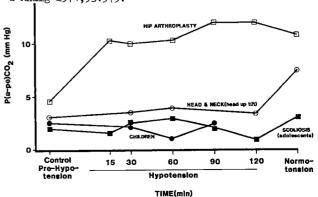
patients undergoing hip arthroplasty, (mean age = 65.5 years) the gradient increased to 10.0 after induction of hypotension and remained between 8.8 and 12.0 mm Hg throughout the hypotensive phase. When patients were divided into two groups according to age rather than procedure (above and below 50 years), we found that older patients had significant and sustained increase in P(a-pe) CO₂ during hypotension. Figure

Discussion. It is apparent from the present and previous investigations that induced hypotension is not uniformly associated with an increased alveolar dead space. Many factors appear to influence the magnitude of change in alveolar dead space during hypotension. These include: degree of hypotension; posture; hemodynamic alterations; filling pressures and cardiac output; presence of pulmonary disease and age. From the present investigation, it appears that age is an important factor influencing dead space change during hypotension. Patients undergoing scoliosis repair did not exhibit an increase in dead space. These findings are in agreement with a previous study in 14 children which demonstrated no change in P(a-pe)CO₂ during deliberate hypotension in the supine or head-up tilt. The increase in P(a-pe)CO, seen in older patients during deliberate hypotension may be attributed to changes in pulmonary function with age and/or pulmonary disease.

Conclusions. 1) Deliberate hypotension is not uniformly associated with increased alveolar dead space. 2) Older patients are prone to develop an increase in dead space during hypotension. 3) Ppe CO₂ provides a reliable estimate of PaCO₂ during hypotensive anesthesia in children and young healthy adults, but not in older patients.

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THE INFLUENCE OF FRESH GAS FLOW AND I/E RATIO ON TIDAL

VOLUME AND PaCO2 IN ANESTHETIZED PATIENTS

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INTRODUCTION: Bench studies have documented that the delivered tidal volume (TV) from a variety of anesthesia ventilators is dependent upon fresh gas flow (FGF). ^{1,2} Similarly, it has been <u>calculated</u> that the inspiratory/expiratory ratio (I/E Ratio) will also influence TV.³ This study was undertaken to define the relative importance of both the I/E Ratio and FGF in determining not only TV, but PaCO₂ in patients undergoing surgical procedures.

METHODS: After institutional review and approval, seven ASA I or II patients undergoing lower abdominal or lower extremity procedures were anesthetized with a variety of general anesthetic techniques and orally intubated. After attainment of a stable anesthetic state and surgical positioning, mechanical ventilation with a Narkomed II anesthesia machine and ventilator was instituted; bellows volume was adjusted to 12 cc/Kg and the rate set at 7 breaths/min. Thereafter, bellows volume was not altered. In all patients, initial FGF was 2 liters/min and I/E Ratio was 1:4.5. After a minimum of 20 min at these settings, expired TV was measured with a calibrated Wright's spirometer and arterial blood gas analysis was performed. I/E Ratio was then changed to 1:2 and all measurements were repeated. FGF was then increased to 6 liters/min and all measurements repeated after appropriate equilibration during ventilation with I/E Ratios of 1:4.5 and 1:2. This entire sequence was then repeated with a FGF of 10 liters/min. In this manner, expired TV and arterial blood gases were measured in all seven patients during all combinations of three levels of FGF (2,6 and 10 liters/min) and two I/E Ratios (1:2 and 1:4.5).

The TV during initial ventilation with I/E Ratio of 1:4.5 and FGF 2 liters/min was established as the Baseline TV. The per cent change in TV from Baseline TV (Δ TV) and absolute PaCO₂ were plotted as a function of FGF for each I/E Ratio (Figures 1 and 2).

The slopes of the lines were compared with a student's t-test. p < 0.05 was considered statistically significant.

<u>RESULTS:</u> Initial PaCO₂ with bellows set at 15 cc/Kg, FGF = 2 liters/min, and I/E Ratio of 1:4.5 was 43 ± 2 mm Hg. Thereafter, Δ TV increased and PaCO₂ decreased with each increase in FGF and with each change from I/E Ratio = 1:4.5 to I/E Ratio = 1:2. PaCO₂ was the lowest with FGF = 10 liters and I/E Ratio = 1:2, being 30 ± 3 mm Hg. The slopes of the lines relating Δ TV to FGF and PaCO₂ to FGF at each I/E Ratio were significantly different.

DISCUSSION: These data demonstrate that both FGF and I/E Ratio are important determinants of TV and PaCO₂ in surgical patients being mechanically ventilated with a fixed bellows volume. The divergent slopes of the lines relating PaCO₂ and TV to FGF at the different I/E Ratios indicate that I/E Ratio becomes a more important determinant of TV and PaCO₂ as FGF increases. The average change in arterial PaCO₂ from 43 to 30

mm Hg over the range of FGF and I:E Ratio studied further indicates that physiologically significant alterations in acid base status can occur despite a constant bellows volume if the relative contributions of FGF and I/E Ratio to minute ventilation are not appreciated.

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FIGURE 1- A TV vs. FGF at different I:E Ratios

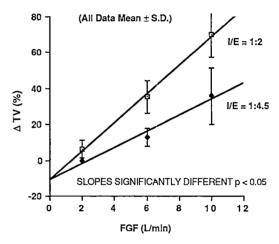
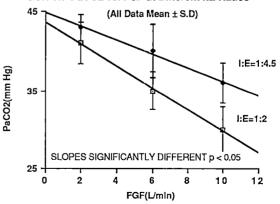


FIGURE 2- PaCO2 vs. FGF at Different I:E Ratios



TITLE:

ALTERED EEG PESPONSE TO ISOFTURANE IN THE ELDERLY

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Introduction. Aging is associated with physiological changes which may alter drug action. Stevens et al reported that for isoflurane the elderly have a greater sensitivity to this anesthetic, as expressed in a reduced minimum alveolar concentration (MAC) 1. It is also known that isoflurane causes EEG burst suppression at doses above MAC. Furthermore, the furation of isoelectricity (electrical silence) increases with increasing dose. This study was lesigned to determine if the increased sensitivity to isoflurane in the elderly is also reflected in changes in EEG burst suppression.

Methods. This study was approved by the Institutional Committee on Research Involving Juman Subjects. Informed consent was obtained from 5 elderly (70-86 years) and 5 younger (23-30 years) patients scheduled for elective surgery. All patients were without neurological lisease and taking no drugs known to alter sensitivity to general anesthetics. Subjects received no premedication other than sodium itrate (30cc) taken orally. General anesthesia as induced by inhalation of nitrous oxide (70%) and oxygen with progressively higher concentraions of isoflurane. Nitrous oxide was then discontinued and succinylcholine (lmg/kg) was given i.v. to facilitate tracheal intubation. hereafter, patients were ventilated with oxygen (5L/min) and isoflurane. The inspired concentraion of isoflurane was adjusted to produce an and-tidal concentration of 1.7%. It was measured y infrared analysis with a Puritan Bennett mesthetic Agent Monitor (Wilmington, Mass.). or each patient the analyzer was calibrated with known quantity of anesthetic gas. Exhaled gas as obtained from a teflon catheter inserted hrough the endotracheal tube and positioned near he carina. End-tidal carbon dioxide tension was aintained between 35 and 42mm Hg and esophageal emperature was kept between 35.5 and 36.2 legrees Celcius. Arterial blood pressure was mintained within 15% of the pre-induction value y intravenous infusion of lactated Ringer's olution or phenylephrine.

After 25 minutes of continuous 1.7 percent nd-tidal isoflurane concentration the electroncephalogram was recorded for 5 minutes prior to urgical stimulation. Bifrontal leads were used ith a Neurotrac monitor (Interspec, Conshohock, a.). Electrode placement was adjusted until mpedences were all below 5000 ohms. The EEG ignal was stored on cassette tape by a Vetters -track recorder (Rebersburg, Pa.) and analyzed rom the output of a Hewlett Packard (Andover, ass.) strip recorder. EEG recordings were nalyzed for duration of electrical silence, which as expressed as a percentage of the total 5 minute tudy period. A comparison of the duration of isolectricity between elderly and younger patients

was made by Student's t-test for unpaired data (two-tailed). P<0.05 was considered statistically significant.

Results. All patients showed EEG burst suppression (alternating periods of electrical silence disrupted by voltage bursts) at 1.7% endtidal isoflurane concentration. However, in the elderly patients the duration of electrical silence was significantly longer than in the younger controls (Table 1).

Discussion. A reduction in anesthetic requirement with aging has been previously reported Those results, however, were obtained by observing motor response to surgical incision. Such a response requires multiple integrated physiological activities involving sensory neurons, spinal cord, brain, efferent neurons and skeletal muscle. The reduction in MAC in the elderly might be due to changes at any or all of these sites. Our results indicate that the elderly have a more profound electrocortical response to isoflurane than younger patients. This reflects a discrete alteration in brain sensitivity with aging.

Previous investigators have described agerelated alterations in cerebral blood flow, cerebral oxygen consumption, cerebral vascular resistance and neuronal density 4,5 Understanding the role these neuronal density 4,5. Understanding the role these changes may play in the increased sensitivity of the elderly to general anesthetics will require further investigation.

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Table 1. Burst Suppression at 1.7% Isoflurane (mean ± SD)

	<u>elderly</u>	young	<u>P</u>
n	5	5	
Age (yrs)	77.8 ± 5.4	27.6 ± 2.7	<0.01
Isoelectric Time (percent)	75.0 ± 13.0	39.9 ± 17.1	<0.01

Title:

EFFECT OF EJECTION FRACTION ON ALPHA1-ADRENERGIC RESPONSIVENESS DURING CORONARY ARTERY BYPASS

GRAFT SURGERY

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INTRODUCTION: Increasing numbers of patients with impaired left ventricular function (ILVF) are requiring coronary artery bypass graft surgery (CABG). Changes in adrenergic responsiveness during heart failure present challenges in the management and care of these patients. Elevated catecholamine levels and β -receptor desensitization occur with heart failure¹, but the function of the α -receptor is less clear. Although α -receptor desensitization has been described in a rabbit model², α -receptor number appears to stay constant in failing human myocardium. We tested the hypothesis that α_1 -acrenergic responsiveness (α_1AR) decreases in patients with ILVF. We also assessed changes in α_1AR during anesthesia and cardiopulmonary bypass (CPB).

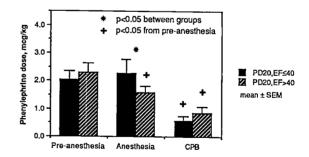
METHODS: After institutional approval and informed patient consent, 34 patients undergoing elective CABG were studied. ILVF was defined prospectively as ejection fraction <40%. Group I consisted of 12 patients with EF \leq 40%; group II consisted of 22 patients with EF \geq 40%. After morphine, scopolamine, diazepam premedication, hemodynamic monitoring was established, baseline measurements recorded, and blood sampled for catecholamine levels. Prior to anesthesia (pre-anesthesia), a pressor dose response curve (PDRC) was generated using a bolus phenylephrine (Phe) technique described as follows. After 20 mcg Phe IV, the maximum mean arterial pressure (MAP) obtained in the subsequent 2 minutes was documented. Five minutes after the first Phe bolus, after MAP had returned to baseline, 40 mcg of Phe was given IV. This was continued at five minute intervals (through the Phe dose range of 20,40,80,120,160,200...mcg) until a 20% rise in MAP was noted. Two additional PDRCs were generated during fentanyl anesthesia (anesthesia), and during CPB (10 minutes after aortic cross clamp). Polynomial regression of PDRCs was used to determine the exact dose of Phe required to increase MAP 20% (pressor dose 20, PD_{20}) and repeated measures analysis of variance with Bonferroni correction to compare groups. RESULTS: PD_{20} was significantly lower (p <0.05) in group II (EF >40%) during fentanyl anesthesia than group I (EF <40%). Hence, more Phe was required to increase MAP 20% in patients with low EF during anesthesia than those patients with EF >40%. There were no significant differences in PD₂₀ values between groups during pre-anesthesia or CPB. Significant decreases in PD20 compared to pre-anesthesia (p <0.05) were seen during CPB in both groups and during fentanyl anesthesia in group II (EF >40%). Therefore, less Phe was required to increase MAP 20% during these time periods compared to pre-anesthesia. These results are summarized in figure 1. There were no significant differences in catecholamine levels between groups. No patient had chest pain or EKG changes during Phe challenges.

CONCLUSIONS:

- 1. α_1AR changes during CABG surgery. This is an important concept since treatment with adrenergic agents (pressors, dilators, inotropes) occurs frequently during cardiac surgery. Modification in doses of α_1 -adrenergic agents may be required during certain periods of CABG surgery.
- 2. α_1 -adrenergic desensitization does not occur in awake (pre-anesthesia) patients with low EF.
- 3. Fentanyl anesthesia, per se, may play a role in $\alpha_1 AR$. Patients with normal ventricular function (EF >40%) required less Phe to increase MAP 20% when anesthetized with fentanyl. However, in patients with EF \leq 40% there was no change in PD_20 with anesthesia. This suggests an element of α_1 -receptor desensitization may have been unmasked by fentanyl.
- 4. α_1AR decreased during CPB in both groups. Less Phe was required during CPB to increase MAP 20% compared to pre-anesthesia. This suggests more powerful effects than anesthesia alone, such as hypothermia, elevated catecholamines, or changes in Phe pharmacokinetics.

FIGURE 1:

Phenylephrine Pressor Dose 20 - EF≤40 and EF>40



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Title: ATRIAL NATURIURETIC PEPTIDE LEVELS IN RESPONSE TO PHENYLEPHRINE PRESSOR CHALLENGE DURING CORONARY ARTERY BYPASS GRAFT SURGERY

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INTRODUCTION: Atrial natriuretic peptide (ANP) is a polypeptide hormone secreted by the heart which induces natriuresis and vasodilatation1. It is released in response to various stimuli including atrial stretch, tachycardia, and vasopressin. ANP levels increase with rewarming during cardiac surgery² and decrease following fentanyl administration in the post bypass In order to further elucidate mechanisms of release of ANP, we tested the hypothesis that pressor challenge with phenylephrine (Phe)

would increase ANP levels.

After institutional approval and patient consent, fifteen patients informed undergoing elective coronary artery bypass surgery (CABG) were enrolled in the study. Routine anesthetic monitors were placed and arterial blood sampled for baseline (pre-Phe) ANP levels with patients resting quietly supine. Phe was then administered every five minutes in increasing bolus doses of 40, 80, 120, 160...mcg, allowing mean arterial pressure (MAP) to return to baseline between each Phe dose. This was continued until MAP increased 20% above baseline. Arterial blood was then sampled for ANP analysis. Central venous pressure (CVP) was kept constant by adjusting fluid infusion during the challenge. ANP was also measured pre- and post-Phe during fentanyl anesthesia following intubation and during cardiopulmonary bypass (CPB) following aortic crossclamp. Plasma ANP levels were measured by radioimmunoassay. The Wilcoxon signed-rank test was used to examine the effect of Phe on ANP. Analysis of variance was used to compare changes in ANP with time (pre-anesthesia, anesthesia, CPB). Significance was declared with <0.05.

Plasma ANP increased significantly RESULTS: (p=0.01) following Phe in awake patients. During fentanyl anesthesia, however, Phe did not affect ANP. A highly significant (p=0.003) decrease in ANP following Phe occurred during CPB. These results are summarized in figure 1. HR decreased 5-15% and pulmonary artery pressure (PAP) increased 10-30% transiently with each Phe bolus during pre-anesthesia and anesthesia. CVP remained constant. Of note, there was no different and the constant. ference in ANP prior to Phe during preanesthesia, anesthesia, and CPB.
DISCUSSION: Several possible mechanisms may

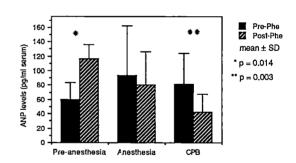
account for increasing ANP after Phe in the awake state. First, HR cannot account for increased ANP release with Phe since HR remained constant or decreased during the challenge. Secondly, although CVP was held constant, changes in atrial dimension may have occurred secondary to the effects of Phe on venous capacitance or PAP causing ANP release. Finally, increased MAP may have contributed to the release of ANP. ANP has been shown to correlate with MAP during CABG2.

Our data suggest that this effect is immediate. Hence, ANP may play a role in the immediate finetuning of blood pressure.

Anesthesia appears to blunt the increase in $\ensuremath{\mathsf{ANP}}$ caused by Phe. Fentanyl anesthesia is known to inhibit catecholamine responses to stress and surgery", and a similar mechanism may blunt the ANP response to a pressor "stress". Of note, fentanyl anesthesia does not affect pre-Pne ANP levels; this contradicts a previous study in seven patients.

Substantial reductions in ANP in response to Phe during CPB may be due to hemodilution, hypothermia or increased catecholamines*. Hypothermia has been shown to inhibit catecholamine release in the venous system and may also inhibit ANP release. Further investigation is needed to elucidate this mechanism since a reduction in ANP following Phe administration during CPB may contribute to post-CPB hypertension.

Figure 1: ANP Levels in Response to Phe Pressor Challenge During Cardiac Surgery



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Title: DOES MEDETOMIDINE DECREASE ANESTHETIC REQUIREMENTS THROUGH BOTH PRE AND POSTSYNAPTIC ALPHA₂ ADRENORECEPTOES?

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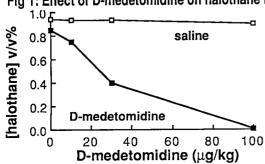
<u>Introduction</u>: Alpha₂ adrenergic agonists, such as onidine, reduce the dose requirements for clonidine halothane Since surgical or neurolytic disruption of central noradrenergic pathways decrease MAC, a likely reason for the anesthetic-sparing action of the $alpha_2$ agonists may be a decrease in central norepinephrine release mediated by the autoinihibitory presynaptic alpha2 adrenoreceptors on noradrenergic neurons. However, other endogenous opioidergic neuromodulators, including purinergic systems may also be responsible for the central nervous system effects of the alpha2 agonists. Clonidine increases central release of endorphin² and is functionally synergistic with adenosine as an inhibitory neuromodulator3. Also, postsynaptic alpha, adrenoreceptors have now been demonstrated in the central nervous system where they can mediate a sedative action4. Thus, the locus for the MAC-sparing effect of alpha2 agonists may not be exclusively presynaptic. Medetomidine is more selective as a full agonist for central alpha₂ adrenoceptors than is clonidine⁵ and is available as both an active (D) and an inactive (L) isomer for the anesthetic-sparing action. We have used the Disomer to probe the mediating mechanism for the MACsparing effect of the alpha₂ agonists in rats.

<u>Methods</u>: Halothane MAC was determined in male

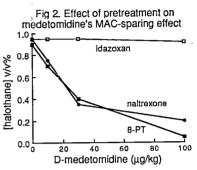
<u>Methods</u>: Sprague-Dawley rats (160-250g) before and after Dmedetomidine (D-med), 10, 30 and 100 ug/kg or saline To determine whether alpha2 adrenoreceptors mediated the MAC-sparing effect of D-med, cohorts of rats (n=6 for each dose) were pretreated with idazcxan(IDA), 10 mg/kg i.p., the highly-selective alpha2 antagonist. To determine whether D-med's MACreducing action was mediated in part through either opiate or adenosine receptors, groups of rats were pretreated with either naltrexone, 5 mg/kg i.p., an opiate antagonist; or 8-phenyltheophylline (8-PT), 2.5 mg/kg i.p., an A_1 adenosine antagonist. To determine whether postsynaptic mechanisms mediate the anesthetic-sparing effect of D-med, rats were depleted of central norepinephrine stores with n-(2-chloroethyl)-n-ethyl-2-bromobenzylamine (DSP-4)⁶ and 4 days later MAC was determined before and after each dose of D-medetomidine. Data were analysed by ANOVA and where appropriate by paired t-test. A P value of < 0.05 was the level for significance. Results: D-med dose-dependently decreased MAC for

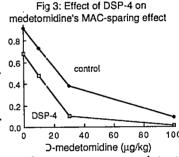
Results: D-med dose-dependently decreased MAC for halothane (Fig 1) such that at the highest dose, halothane could be discontinued for up to 60 min without eliciting a response to tail-clamping.

Fig 1: Effect of D-medetomidine on halothane MAC



completely IDA prevented the MACreducing action of while D-med. naltrexone and 8-PT were without effect (Fig 2). The DSP-4 lesioned rats had a basal MAC lower than the saline controls (Fig 3); nafter however there was a profound still reduction MAC. halothane Discussion: These data indicate that D-medetomidine's potent MAC-sparing action (Fig 1) is § through ≥ mediated alpha2adrenoreceptors with no recapparent involvement of either receptors opiate or A₁adenoreceptors. Data from the DSP-4





lesioned-rats, before D-med treatment are consistent studies which demonstrated earlier significant reduction in MAC (up to 40%) when noradrenergic pathways are disrupted. However the extent to which D-medetomidire reduces halothane MAC (- 100%) and the fact that D-med is still able to reduce halothane MAC in norepinephrine-depleted rats, indicate that the mediating mechanism must involve site(s) in addition to the auto-inhibitory presynaptic alpha2 adrenoreceptors on noradrenergic neurons. We speculate that central postsynaptic alpha₂ adrenergic receptors also mediate anesthetic action of the alpha2 adrenergic agonists. References:

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ABSTRACTS

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TITLE: CARDIOVASCULAR EFFECTS OF PIPECURONIJM BROMIDE UNDER BALANCED ANESTHESIA

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INTRODUCTION Pipecuronium bromide (PIP) is a new steroid-type nondepolarizing muscle relaxant with a duration of action similar to paneuronium but reported to have minimal cardiovascular side effects. 1,2 Foldes et al, demonstrated a decrease in heart rate (HR) after 43 µg/kg of PIP. 1 In patients scheduled for CABG, Tassonyi et al, showed a fall in HR after 50 $\mu g/kg$ bolus of PIP but no change following 100 $\mu g/kg$ nor 150 $\mu g/kg$. They also demonstrated a fall in cardiac index but no change in stroke volume index at doses of 100 µg/kg and 150 μg/kg. Nguyen et al showed no change in HR when PI³ was given with enflurane. 3 Our study evaluates cardiovascular effects of PIP on patients having non-cardiac surgery under balanced anesthesia. Three dosages of PIP were selected to cover the range two to three times its ED90. METHODS 30 ASA physical status I-III patients gave written informed consent to participate in this IRB approved study. All patients received morphine (0. mg/kg) and atropine (0.4 mg) IM as premedication. Anesthesia was induced with fentanyl (3-6 µg/kg) and thiopental (3-6 mg/kg). N₂0/0₂ (60/40) was administered by mask prior to PIP injection. Patients (10 per group) were randomly assigned to receive either 70, 85 or 100 $\mu g/kg$ bolus of PIP over five seconds. HR, systolic (BPs), and diastolic (BPd) blood pressure were determined via an automated cuff (Dinamapp). Cardiac output (CO) was measured by a non-invasive doppler technique (Lawrence 3000). This method utilizes an ultrasonic probe placed at the sternal notch to measure blood velocity at the aortic root. The instrument calculates CO as the product of blood velocity and aortic root area as determined by a nomogram. All CO values were the mean of at least two recordings. Hemodynamic data were obtained whem patients were awake, two to three minutes postinduction but pre-PIP, and one and two minutes post-PIP. Statistical analysis was performed by one-way ANOVA for repeated measures. A p<0.05 was considered significant. All results are reported as means $(\pm S.D.)$.

RESULTS The patients in this study ranged between 22 to 63 years old and weighed from 48 to 100 kg. These variables were not significantly different between the groups. Only two patients, one in the 85 $\mu g/kg$ group and one in the 100 $\mu g/kg$ group, were taking cardiovascular medications pre-operatively. The analysis of cardiovascular data showed no significant differences among the groups over time. Therefore, data for the groups were pooled. Induction resulted in a drcp of BPs from a mean of 138.4 (18.6) mmHg to a mean of 121.4 (21.9) mmHg, p<0.01. BPd decreased from a mean of 72.4 (12.4) nmHg to 66.4 (16.5) mmHg, p<0.01. HR increased from a mean of 78.3 (19.7) bpm to 83.6 (17.3) bpm, p<0.05. The CO did not change significantly with induction, [5.5 (1.4) to 5.4 (1.5) L/min]. Administration of PIP led to a significant decrease in HR at one and two minutes but no change in CO

was detected (Table I). This was, however. accompanied by significant decreases in BPs and BPd (Table II).

DISCUSSION Our data confirms previous reports of HR slowing following PIP. In addition, under balanced anesthesia, we found significant decrease in BPs and BPd following administration of two to three times the ED_{90} of PIP. Changes in blood pressure following administration of PIP were similiar to those seen with induction. CO data did not show significant change. It should be noted, however, that the doppler CO determination may not be sensitive enough to detect five to ten percent changes. Since PIP was not administered until two to three minutes after induction and no further anesthetic drugs were given during this period, we feel the hemodynamic changes may not totally be due to extended effects of the induction drugs. The hemodynamic changes observed in this study could also represent the effects of PIP. However, since no change in HR is reported after administration of PIP under enflurane anesthesia3, it appears that fentanyl may also contribute in lowering of HR. Exact contribution of PIP on HR changes needs further clarification. In conclusion, while the NM blocking effect of FIP is similar to pancuronium, the cardiovascular actions of PIP are more like vecuronium.

Table I - Hemodynamic Parameters from Pooled Data n=30

	HR(bpm)	CO(L/min)
Pre-PIP 1 min Post-PIP 2 min Post-PIP	83 (17.3) 76 (15)* 75 (16)*	5.4 (1.5) 5.3 (1.6) 5.3 (1.6).
	*p<0.01 <u>vs</u> . Pre-PIP	NS

Table II - Hemodynamic Parameters from Pooled Data

	BPs(mmHg)	BPd(mmHg)	
Pre-PIP 1 min Post-PIP 2 min Post-PIP	121 (21.8) 107 (19)* 105 (19.2)*	66 (15) 60 (13.8)* 58 (12.2)*	
	*p<0.01 <u>vs</u> . Pre-PIP	*p<0.01 vs	

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TITLE:

LOWER ESOPHAGEAL CONTRACTILITY PREDICTS MOVEMENT DURING SKIN INCISION; VECURONIUM

DOES NOT DECREASE THE MAC OF HALOTHANE

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Introduction. The frequency of spontaneous lower esophageal contractions (SLEC) has been proposed as a measure of anesthetic depth. The present study determined whether SLEC frequency could predict movement in response to skin incision. Because the MAC of halothane is reduced 25% in patients paralyzed with pancuronium,2 we used this opportunity to determine whether vecuronium also decreases the MAC of halothane.

Methods. Following approval of the Committee on Human Research, we determined the MAC of halothane in twelve patients paralyzed with vecuronium. Unpremedicated ASA I or II patients (age: 24-63 years) scheduled for abdominal or perineal surgery were studied. Following induction of anesthesia with N2O and halothane only, orthopedic tourniquets were placed on one arm and both legs of each patient and inflated to 300 mmHg. Nitrous oxide was discontinued within three min of induction. Vecuronium (0.1 mg/kg) was administered intravenously, and each patient's trachea was intubated. End-tidal halothane, determined by mass spectrometry, was then adjusted to a concentration determined by the Dixon "up-and-down" method (the interval used was 0.1% and four patients comprised each group). Constant end-tidal halothane concentrations were maintained at least 15 min before skin incision. Halothane concentrations were corrected for age using a factor of 0.84 in patients > 55 years and a factor of 1.1 was used in those < 30 years.3 A peripheral nerve stimulator confirmed isolation of the extremities from circulating vecuronium. A positive response was defined as a gross, purposeful movement occurring within 1.5 min of skin incision. Spontaneous contractions in the lower esophagus were evaluated using the Lectron® 302 monitor (American Antec Inc.). The esophageal probe was positioned ≈ 35 cm from the teeth and then adjusted to maximize heart sounds. Water volume in the pressuresensing balloon was adjusted until the baseline pressure was 3-5 cm H_2O , and threshold sensitivity was set to 15 cm H_2O . The predictive value of SLEC frequency was tested using the log-likelihood ratio.4 The MAC of halothane was compared with previously reported values using an unpaired, two-tailed T-test. P < 0.05 was considered significant.

Results. Figure 1 plots the number of patients moving and not moving in response to skin incision at different end-tidal halothane concentrations. The MAC of halothane was 0.78 \pm .08 (SD). In figure 2, movement after skin incision is plotted against the number of SLEC occurring during the 6 min prior to incision. With only one exception, patients having no SLEC in 6 min preceding incision did not move whereas those demonstrating ≥ 2 SLEC in 6 min moved following skin incision (P < 0.025).

Discussion. The MAC of halothane in patients paralyzed with vecuronium did not differ from that in unparalyzed patients (P > 0.05).^{2,3} These results contrast with those obtained in patients paralyzed with pancuronium in whom MAC is decreased 25%.2 An explanation based on differences in study techniques seems unlikely since the methods used in each study were similar. Thus, these structurally similar muscle relaxants appear to affect anesthetic requirement differently. Movement following skin incision was reliably predicted by a SLEC frequency ≥ 2 per 6 min whereas absence of SLEC predicted absence of movement. Esophageal contractility appears to be a useful indicator of anesthetic depth.

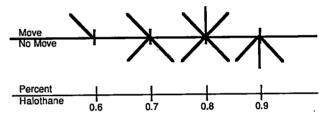


Fig. 1. The number of patients moving and not moving in response to skin incision at different end-tidal halothane concentrations. Each line represents one patient.

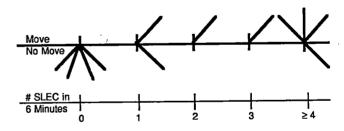


Fig. 2. The number of patients moving and not moving in response to skin incision at different spontaneous lower esophageal contractility (SLEC) frequencies. Each line represents one patient.

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TITLE:

THE THERMOREGULATORY THRESHOLD IN HUMANS DURING HALOTHANE ANESTHESIA

Authors:

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Introduction. The extent to which thermoregulation is active during anesthesia is unknown.1 patients undergoing ophthalmic surgery, similar changes in core temperature occurred during halothane/O2 and N₂O/fentanyl anesthesia.² During both anesthetics, core temperatures decreased to 36.2°C after 2 h, and we're constant for the remainder of surgery. Thermal steady state occurs when heat loss to the environment equals metabolic heat production; it is likely that steady-state temperatures in these relatively normothermic patients resulted from a passive interaction with the environmen: (no active thermoregulation). However, this thesis does not exclude the possibility that steady state in sufficiently hypothermic patients might result from active thermoregulatory vasoconstriction and/or nonshivering thermogenesis. The present study tested whether thermal steady state results from active thermoregulation (profound cutaneous vasoconstriction) in hypothermic patients.

Methods. Following approval of the Committee on Human Research, ten, unpremedicated, ASA I or I patients (age range: 26 — 57 yrs) undergoing livingrelated donor nephrectomy were anesthetized with 1% halothane/O2. Patients were randomly assigned c standard treatment (no hypothermia precautions) or maximum warming measures (warm fluids, warming blanket, humidifier, warm room). Esophageal temperatures and skin surface temperature gradien-s (forearm — fingertip) were measured with disposable Mon-a-Therm® thermocouples. Skin temperatures were measured on the non-dependent arm which was exposed o room air and did not have an intravenous catheter er plood pressure cuff. Cutaneous blood flow is known to reflect central thermoregulation,3 and skin temperature gradients correlate well with other measures of vasoconstriction^{4,5} and are minimally affected by ambient emperature.⁶ The thermoregulatory threshold was prospectively defined as the esophageal temperature associated with a skin temperature gradient ≥ 4°C. Typical skin temperature gradients during anesthesia are 2°C (fingertip warmer than forearm).

Results. Normothermic patients [36.2 ± 0.2°C SD)] demonstrated no significant vasoconstrictior. lowever, each hypothermic patient displayed asoconstriction at esophageal temperatures ranging rom 34.0 to 34.8°C [average: 34.5 ± 0.2°C (SD)] (Fig.). Vasoconstriction occurred at 125 \pm 24 (SD) min after nduction and core temperatures did not decrease further ollowing vasoconstriction.

Discussion. Significant vasoconstriction was bserved in hypothermic patients, but not in normothermic atients undergoing similar surgery. Our data indicate hat vasoconstriction in hypothermic patients results from

active thermoregulation rather than hypovolemia or surgical stress. Vasoconstriction effectively decreased heat loss to the environment and prevented further hypothermia. Consequently, thermal steady state in the hypothermic patients resulted from active thermoregulation. This finding contrasts with that in nearnormothermic subjects undergoing ophthalmic surgery in whom thermal steady state appeared to result from a passive interaction with the environment. The technique used in the present study, measurement of skin-surface temperature gradients, is an effective, quantitative method of determining the hypothermic threshold temperature during anesthesia.

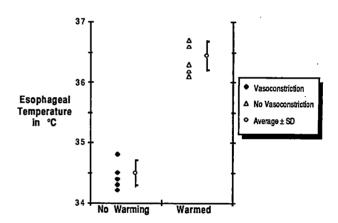


Figure 1. Significant vasoconstriction was observed in 5 patients who became hypothermic during donor nephrectomy patients who became hypothermic during donor nephrectomy surgery. Vasoconstriction did not occur in 5 other patients maintained normothermic. Thermoregulatory vasoconstriction was prospectively defined as a skin-surface temperature gradient (torearm temperature — finger tip temperature) \geq 4°C. The thermoregulatory threshold during surgery with halothane anesthesia is 34.5 \pm 0.2°C (SD).

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Supported by grants from the Pharmaceutical Manufacturers Association Foundation, the UCSF Committee on Research Evaluation and Allocation, and Mon-a-Therm® Inc.

TITLE:

PRESENCE OF CARBON MONOXIDE IN ANESTHESIA CIRCUIT WITH LASER BRONCHOSCOPY: A NEW HAZARD

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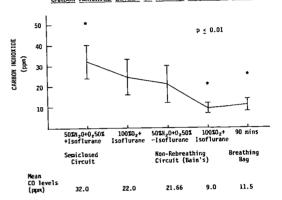
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Introduction: Bronchoscopic excision of tracheobronchial lesions by carbon dioxide laser energy has emerged as an effective palliative procedure. A beam of laser energy vaporizes tissue through the bronchoscope. We were concerned with the effects of carbon monoxide production from burning tissue on the inspired oxygen concentrations administered as part of anesthetic maintenance. Incomplete combustion during laser excision could produce unacceptable carbon procedures monoxide concentrations for patients.

Methods and Materials: We undertook to study

the relationship of two widely used anesthetic circuits to carbon monoxide levels produced with two different fractions of inspired oxygen concentration. Three patients (ASAIII) undergoing laser bronchoscopy were studied. Informed consent was obtained from the patients and approval for the study had been obtained from the Institutional Review Board. Each patient was premedicated with diazepam 10mg p.o. 90 minutes prior to surgery. All had standard routine monitoring. Usual and customary Laser precautions were carried out eyes lubricated and taped with wet eye patches; OR personnel goggles were provided, etc. Following induction, a Wolffe cuffed bronchoscope (water filled) was inserted in the trachea. All patients were paralyzed with pancuronium and were given 2-5 $\mu g/kg$ of fentanyl intravenously; an anesthetic gas mixture was then directed through the side arm of the bronchoscope. Carbon monoxide was measured in parts per million in air using chromotography strips specific for carbon monoxide. All patients were then maintained (a) for 10 minutes with a semiclosed circuit 50% 0_2+N_20+ potent inhalation agent followed by (b) for 10 minutes $100\%, 0_2+$ potent agent. A non-rebreathing circuit (Bain's) was then substituted to maintain anesthesia and subsequent measurements were made (c) after 10 minutes of 50% 0_2+N_2 0+potent inhalational agent and (d) after $10\,$ minutes of $100\%\,\,0_2$ with potent inhalational agent. Carbon monoxide levels were determined at the midtrachea level after each of these time intervals as well as from the breathing bag after after 90 minutes of surgery.

Results: Carbon monoxide levels were found to be inversely proportional to oxygen concentrations delivered when the above results were plotted. Recommendations resulting from our study include the use of a Bain's circuit with 100% O₂ plus potent inhalation agent in a paralyzed patient to (1) Minimize production of carbon monoxide (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation (2) Prevent accumulation of carbon monoxide and avoid small inhalation agent in a paralyzed patient (2) Prevent accumulation of carbon monoxide (2) Prevent accumulation of carbon monoxide (3) Prevent accumulation of carbon monoxide (4) Prevent accumulation accumula monoxide and avoid smoke inhalation (3) Decrease or eliminate the inspired carbon monoxide level and (4) Maintain paralysis for these anesthetized patients thereby reducing their 0_2 consumption. Carbon monoxide was determined to be 11.5 ppm in the breathing bag after 90 minutes despite numerous circuit disconnects. CARBON MONOXIDE LEVELS IN VARIOUS ANESTHESIA CIRCUITS



Discussion: As in any other form of Laser surgery, bronchoscopy with same necessitates all precautions for fire and misfire from the laser beam. Carbon monoxide was detected as part of the "smoke" rising during laser surgery. Even though the amount detectec was extremely small, very little is known about carbon monoxide toxicity at low levels² and there is nothing in the literature about carbon monoxide during anesthesia. Recommendation for the use of a non-rebreathing circuit with 100% oxygen plus a potent inhalation agent theoretically avoids rebreathing of "smoke inhalation". Delivery of 100% oxygen is necessary as it reduces carbon monoxide production along with improved oxygen carrying capacity; it is also the first line of treatment for carbon monoxide toxicity in the reduction and elimination of carbon monoxide. Potent inhalation agents along with a paralyzed patient during Laser surgery are essential for the following reasons: to reduce oxygen consumption whereby acquisition of carbon monoxide by the patient is reduced; to reduce the bronchospastic element in these patients; and to enable the surgeon to aim the laser beam precisely at the target. A decrease in mucociliary movement is common postoperatively secondary to the tumor itself, anesthetics, thermal injury from laser beam impact and saline irrigation used to lower the temperature at the site of surgery. Carbon monoxide was measured at a position where it was likely to be inspired after one minute in a semiclosed circuit. Cumulative toxic effects carbon monoxide could be detrimental in a

semiclosed circuit with a low FiO₂ even if of short duration in critically ill patients.

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Title:

REGIONAL CEREBRAL BLOOD FLOW IN 14LIGNANT SUPRATENTORIAL TUMORS VS NORMAL BRAIN

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Introduction: Intracranial hypertension is a well-recognized complication in the perioperative management of patients with malignant supratentoria_ brain tumors of every cell-type, and this always is a serious concern with regard to optimal anesthetic care. The compromised intracranial compliance caused by these tumors could be based on at least two possible mechanisms. One possibility is that toe tumor causes an expanding mass-effect that gradually exhausts the pressure-volume reserves of the cranial compartment such that a relatively small increase r cerebral blood volume within normal brain might produce a large increase in ICP. An alternative possibility is that impaired cerebrovascular react:vity in the tumor mass might result in large imcreases in cerebral blood flow and consequent intracranial hypertension whenever arterial blood pressure or CO₂ tension increases. To our knowledge these two possible mechanisms for intracranial hypertension have not been studied in a systematic fashion, although both are often invoked whenever ICP problems are discussed in managing malignart supratentorial tumors.

Recently, the availability of Laser-Doppler Velocimetry (LDV) has facilitated the measurement cf regional cerebral blood flow in a variety of pathclogical states. LDV is an optical method that derives local blood flow from the mean Doppler shift imparted to laser light as erythrocytes move through a capillary network. Its output is a "flow index" that reflects the mean frequency of the Doppler-shifted light and is linearly related to tissue blood flow.

We have applied this technology to correlate changes in blood flow in brain tumors with normal brain blood flow during general anesthesia for craniotomy and tumor excision.

Methods: 5 patients with malignant supratentorial tumors (3 gliomas, 2 metastatic lesions) have been the subjects of this investigation thus far. The protocol was approved by the local Institutiona. Review Board and informed consent for the study was given by the patient or their nearest relative General anesthesia was induced with a thiopentalnitrous oxide-vecuronium sequence supplemented with either fentanyl, 3-8 µg/kg, or isoflurane, 0.45 and-tidal concentration. Controlled ventilation vas instituted to maintain PetCO₂ at approximately 25 mm Hg. After a wide craniotomy flap had been turned and the brain cortex had been exposed, a laser-spectroscopy flow probe was alternately placec

over normal brain and over the brain tumor.

Blood flow determinations were made during the following sequence of perturbations: 1) During hypocarbia with blood pressure normal; 2) During normocarbia with blood pressure normal; 3) During normo-carbia with blood pressure elevated by infusion of 0.1% phenylephrine solution. Statistical comparisons between normal brain and tumor blood flow were performed using student's t-test for paired data. P<.05 was regarded as significant.

Results: Our results are summarized in table 1. Since the numerical factor for converting LDV output to cerebral blood flow has not yet been determined for human brain, all data for tumor blood flow are tabulated as a percentage of the flow determined in the same patient's normal cortex during normotension and normocarbia.

TABLE 1

Blood Pressure (mm Hg)	PaCO _n (mm Hg)	Normal Cortex	Tumor
88 <u>+</u> 5	38 <u>+</u> 1	100	19 <u>+</u> 7*
83 <u>+</u> 4	28 <u>+</u> 1	88 <u>+</u> 32	29 <u>+</u> 15*
137 <u>+</u> 2	39 <u>+</u> 1	96 <u>+</u> 7	20 <u>+</u> 9*
All Values: M	ean <u>+</u> S.E.	*	= P<.05

Discussion/Conclusions: These observations indicate that blood flow through malignant supratentorial brain tumers is often only a small fraction of normal cortical cerebral blood flow. Furthermore, in the tumors examined thus far, blood flow does not change markedly with increases in arterial pressure above normal values, nor does it change vith reduction of arterial CO₂ tension. In contrast, cerebral cortex in the vicinity of malignant brain tumors appears to retain both autoregulatory capacity and CO₂ responsiveness. These data support the thesis that intracranial hypertension occurring before and during operations for malignant supratentorial tumor resection results from compromised intracranial compliance due to the mass effect of the tumor, and not because of impaired vascular reactivity to CO₂ or arterial pressure within the tumor itself.

Title: REQUISITE FRESH GAS FLOWS FOR THE BAIN AND ADE CIRCUITS DURING CONTROLLED VENTILATION IN ADULTS.

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Introduction: The Bain circuit and Humphrey's "A.D.E." circuit are relatively recent modifications of the traditional Mapleson anesthesia circuits. Both have been reported to function well in adult patients during controlled ventilation when a fresh gas flow (FGF) of 70 ml/kg/min is utilized, although it is well recognized that such a high flow of expensive gases is exceedingly wasteful. In a recent study we found that the Bain circuit could maintain normocarbia during controlled ventilation in adults with a FGF of only 40 ml/kg/min. We undertook the present investigation to compare the efficiency of the Bain circuit with that of the Mapleson D mode of the "A.D.E." system during controlled ventilation in adults.

Methods: The subjects were 20 healthy adult patients undergoing elective surgery. This study was approved by the Institutional Review Board and all patients gave informed consent. Anesthesia was maintained with an 0_2 - N_2 0-isoflurane mixture after endotracheal intubation. Inspired and end-tidal gas concentrations for CO₂, O₂, N₂O and isoflurane were monitored with a mass spectrometer sampling from the endotracheal tube. VE was determined with a Wright respirometer placed at the endotracheal tube. After establishing normocapnia with a circle absorber system, patients were randomly assigned either to a Bain circuit or to the A.D.E. circuit. The patients then were switched to the other circuit, so that each patient served as his/her own control.

Cardiovascular and respiratory measurements were performed at the following times: 1) after 30 min of stable anesthesia using a Drager Narcomed II circle system with VE adjusted to maintain PETCO₂ at 35-40 mm Hg. 2) After 30 min with either Bain of ADE circuit using the same VE as step 1, but with a FGF rate sufficient to keep PETCO₂ between 35-40 mm Hg. 3) After 30 min using the other circuit with the same VE as step 1 and the same FGF rate as step 2. 4) 30 min after return to the circle system with the same FGF rate as step 3 and the same VE as step 1. A single arterial blood sample was analyzed just before the end of each step. Statistical comparisons were performed using analysis of variance with p<.05 regarded as significant.

Results: Our results are summarized in the figure. In step 1 the required VE for these patients was determined to be 58 ml/kg/min ± 2 (mean ± SE). The patients who were put on the Bain circuit first required a FGF of 54 ml/kg/min ± 2 to maintain a PETCO₂ of 35-40 mm Hg. Those using the ADE circuit first required a significantly higher FGF of 67 ml/kg/min ± 3 to maintain the same PETCO₂. Furthermore, at the same FGF rate, when the circuits were changed from Bain to ADE, the end-tidal CO₂ increased significantly. In contrast, the reverse tended to occur when patients were changed from the ADE to the Bain circuit, although this change was not statistically significant. The corresponding PaCO₂ value during use of the Bain circuit was 42.6 mm of Hg ± 0.6, and this increased to 44.7 mm of Hg ± 1.0 (p<.05) when the ADE circuit was utilized. Patients who were randomized to the ADE circuit first had a PaCO₂ of 45.3 mm Hg ± 0.8 initially, but this decreased to 43.7 mm of Hg ± 0.9 when they were changents.

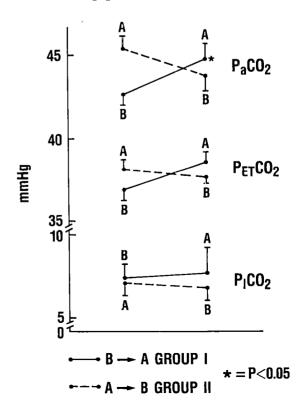
ed to the Bain circuit (NS). No change in heart rate, BP, inspired or end-tidal isoflurane concentration was observed during the study.

<u>Discussion/Conclusions</u>: In this carefully-controlled randomized study we found that the Bain circuit is more efficient than the ADE circuit and that significant savings in FGF can be realized during controlled ventilation if end-tidal CO₂ tensions are monitored to ensure patient safety. While the ADE circuit has the advantage of being able to convert easily from the Mapleson "D" mode to the Mapleson "A" mode when a patient's breathing becomes spontaneous, we conclude that the ADE circuit is not as efficient as the Bain circuit in conserving expensive anesthetic gases during a prolonged operation using controlled ventilation.

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DIFFERENTIAL CO₂ TENSIONS BETWEEN ADE [A] AND BAIN [B] CIRCUITS



Title: "DELTA - SHIFT": AN EEG SIGN OF WKAKENING DURING LIGHT ISOFLURANE ANESTHESIA

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Introduction: The problem of detecting awareness under anesthesia in the paralyzed patient remains unsolved. Cardiovascular signs are notoriously unreliable, and predictable EEG parameters indicative of consciousness have yet to be described. Although a variety of derived numeric descriptors have been used to quantify the EEG, none is yet reliable. While the presence of fast EEG activity in the alpha and beta range (8-26 Hz) is thought to be necessary for awareness, lately we have been impressed with the changes that occur in delta activity (0-4 Hz) during emergence from anesthesia. This study addresses the early detection of awareness by using the ratio of power in the alpha and beta frequency range to that in the delta range in order to predict awarening as patients emerge from isoflurane anesthesia.

Methods: The subjects were 10 adult patients undergoing routine elective surgery. This study was approved by the Institutional Review Board. Anesthesia was maintained with isoflurane in 02-N20 after endotracheal intubation. All patients were mechanically ventilated to maintain end-tidal carbon dioxide between 35-40 mm Hg. No narcotics were given during the operation. N20 was discontinued long enough before the end of surgery so that only the effects of isoflurane were being observed. At the end of the surgery patients were allowed to emerge from isoflurane without being disturbed except that they were asked to open their eyes every few seconcs until they could follow this command. Inspired and end-tidal gas concentrations for CO2, O2, N2O, and isoflurane were monitored with a mass spectrometer sampling from the endotracheal tube.

Using bilateral fronto-mastoid electrodes, the EEG was recorded continuously and subjected to spectral analysis using an unmodified Tracor-Northern NOM&D EEG processor with stock software. EEG data were recorded on-line and stored on disc for off-lire quantification. EEG power-spectrum data were processed in 4-second epochs by deriving the ratio of power in the delta range (0-4) to the power in the following frequency bands: 1) alpha (8-13 Hz), 2) alpha and beta (8-26 Hz) and 3) alpha, beta and theta (5-26 Hz). Since there is evidence that high frequency artifact from muscular activity (>20 Hz) may interfere with EEG data, we analyzed these same ratios using both 8-20 and 8-26 Hz.

Results: Figure 1 is a representative record of EEG power frequency data during emergence from isoflurane. Arrow #1 indicates the point at which the delta power markedly shifts. Arrow #2 shows where the patient opened his eyes on command. Because of the potential clinical usefulness of this change in delta power as an index of near-consciousness, we calculated the mean value for the above ratios over 10 epochs before and 10 epochs after the observed shift. Similar calculations were made for the 10 epochs before isoflurane was turned off and for those just before the patients opened their

eyes. We found the ratio of alpha and beta power to delta power to be the most consistent among those examined, and these data are therefore, presented.

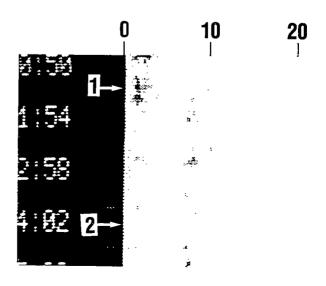
40-Sec Time Period	$\frac{(8-26 \text{ Hz})}{(0-4 \text{ Hz})}$	(8-20 Hz) (0-4 Hz)
Isoflurane off	1.76 ± 0.3	1.56 ± 0.28
Before delta shift	3.58 ± 0.77*	2.84 ± 0.63*
After delta shift	5.31 ± 0.92*	3.66 ± 0.58*
Opened eyes	5.70 ± 0.71	3.86 ± 0.37

All values: Mean + SE * = P<.05 versus previous data point

The mean end-tidal concentration of isoflurane was 0.46 \pm 0.09 volume % when isoflurane was discontinued, and 0.14 \pm 0.01 volume % when patients opened their eyes. The mean time between eye opening and the delta shift point was 3.2 minutes. The overall time from discontinuation of isoflurane to awakening was 8.3 \pm 0.9 minutes.

Discussion/Conclusions: The ratio of EEG power in the delta frequency range to that in higher frequencies appears to be a useful tool for identifying stages of isoflurane anesthesia. In particular, our results demonstrate that it can be used to detect EEG activity indicative of a near-conscious state. This has obvious implications for the prevention of awareness during light levels of isoflurane anesthesia.

Frequency (Hz)



MONITORING SURGICAL STRESS BY SPECTRAL ANALYSIS OF ARTERIAL PRESSURE VARIATIONS Title:

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Introduction: Surgical circulatory responses often characterized by hypertension and tachycardia. However, reflex cardiovascular responses are complex processes mediated by the sympathetic and parasympathetic systems which provide a delicate balance. Arterial pressure (AP) especially is maintained within a relatively normal range by the series of positive and negative feedback loops. Therefore, surgical stress may elicit perturbations of AP with or without causing detectable hypertension. These perturbations of AP can be characterized by applying spectral analysis of AP variation (APV). In this study we observed a series of spectral patterns of APV occurring during surgery and related the pattern to surgical stimuli.

Methods: Five patients, ages 15 to 25 and ASA classification I or II undergoing spine surgery, were studied with institutional approval. All patients were monitored with ECG, radial artery pressure and Swan-Ganz catheterization. The output of the arterial pressure monitor was fed into an IBM AT computer. Power spectra of mean arterial pressure within a period of 256 seconds were computed using a fast Fourier transform after filtration of frequencies outside of 0.02 to 0.5 Hz. A series of power spectra were displayed on a computer screen every 30 seconds. The patients were anesthetized with fentanyl (15-22 g/kg) and nitrous oxide in 35% oxygen. Observations of APV were made during the following 3 states: S1-preinduction, S2-under anesthesia without surgical stimuli and S3-under anesthesia during surgical periosteal stimulations. Spectral properties of mean arterial pressure variations were divided into 4 ranges: APV-1 at 0.02-0.04 Hz, APV-2 at 0.04-0.08 Hz, APV-3 at 0.08-0.12 Hz, APV-4 at 0.12-0.2 Hz. Totals of 20 samples were taken during each state. Significance between the states were analyzed by student t test and P<0.05 was considered significant.

Results: The mean values of spectral peaks (mmHg²/Hz) at each state are shown in Table 1 and typical spectral patterns are shown in Figure 1. 1) When the patients were sedated, but conscious (S1), there was a characteristic pattern of APV with most variations at 0.02 and 0.08 Hz. 2) When the patients were anesthetized, APV decreased except respiratory related variations at about 0.2 Hz. 3) Surgical stimulation elicited slow oscilation of mean arterial pressure mostly at the range less than 0.04 Hz, but there were no significant changes in fast frequency variations related to respiration.

Discussion: Cyclic variations of AP with respiration is well known. Hyndman and Kitnay related mid-frequency (0.1-0.15 Hz) variations to baroreceptor reflex and low frequency (0.04-0.08 Hz) variations to thermoregulatory fluctuations in vasomotor tone. Low frequency APV has been reported following cardiopulmonary bypass, but its

mechanism and clinical importance has not been clear. We have observed that low frequency APV occurred in anesthetized patients associated with surgical stimuli and we interpreted these variations reflected autonomic responses to surgical stress. Anesthetic agents modify these responses. It appears that fentanyl anesthesia shifts the spectral peaks of the stress responses to the slower frequency ranges. Spectral analysis of AP can be a useful measure to monitor surgical stress and ability of anesthetic to block stress in anesthetized patients.

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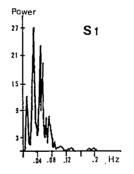
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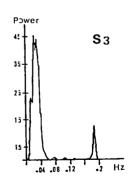
Table 1

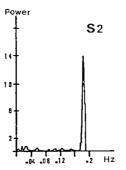
Tan	TG I			
	<u>AP</u> V-1	APV-2	APV-3	APV-4
S1	28.8 <u>+</u> 14.9	28.7 <u>+</u> 22.0	1.8 <u>+</u> 1.6	1.4 <u>+</u> 0.5
S2	3.2 <u>+</u> 3.0*	0.4 <u>+</u> 0.2*	0.4 <u>+</u> 0.2*	12.6 <u>+</u> 6.8*

S3 35.2±22.0⁺ 2.0+1.3^{*} 0.9+0.5 10.5+6.2^{*} * significant as compared to S1 + significant as compared to S2

Figure 1







Citle: RESPIRATORY COMPLIANCE MEASURED BY VOLUME RECRUITMENT IN CHILDREN ANESTHETIZED WITH HALOTHANE

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Introduction. Total respiratory compliance (Crs) as conventionally been measured in children during mesthesia with muscle paralysis by inflating the ungs with a known quantity of gas via an endoracheal tube and measuring airway pressure under tatic conditions (1). This invasive technique is not muitable for children breathing spontaneously from a naesthetic mask. A new technique, termed "volume ecruitment", has been developed for measuring Crs a sedated infants who are breathing from an anesthetic mask (2). We have applied this technique o infants and young children during halothane nesthesia in order to gather information, not reviously available, on Crs during spontaneous reathing with halothane.

Methods. Following approval of the protocol by he Helsinki committee of this hospital, and with nformed consent from the parents, 10 ASA class I hildren from ages 1 month to 3 years were tested uring anesthesia immediately prior to elective urgery. They received pre-anesthetic sedation with riclofos and were anesthetized with 1.5 to 2% alothane in oxygen during continuous ECG and xygen saturation monitoring. They breathed pontaneously from a Rendall Baker mask sealed to he face with soft silicon putty. A pneumotachograph as attached to the mask for measurement of flow nd volume, and mask pressure (Pm) was measured rom a side-port. A T-piece apparatus incorporating wo uni-directional valves, which ensured one-way low, was attached to the pneumotachograph, and the nesthetic apparatus was attached to the inspiratory ort of the T-piece. During spontaneous breathing, he expiratory port of the T-piece was occluded, and he subject could therefore inspire from the nesthetic circuit, but was totally occluded in xpiration. Throughout 4 or 5 respiratory cycles, e progressively recruited volume during inspiration. nd, during attempted expiration, relaxed his espiratory muscles as shown by a plateau on the Pm ignal. This plateau Pm (P) and the corresponding aspired volume (V) were used to plot a V.P curve rom which Crs was calculated. Intra-subject ariability was determined by calculating Crs of ne individual volume recruitment maneuvers for each ubject and determining the CV (s.d./mean) of the ive or more maneuvers in each child.

Results. There were no changes in the clinical ondition of the subjects, or in the monitored arameters, including oxygen saturation, during the sasurements. V.P curves were obtained with similar

correlation coefficients when analysed by linear, polynomial, or parabolic equations. Therefore Crs was calculated as the slope of the linear regression of the V.P data for each child. Individual Crs values correlated with the height of the child (Figure 1) according to the equation:

 $Crs(ml/cmH_2O) = 0.33xHeight(cm) - 14.0, r=0.94$ Intra-subject CV for Crs was 14.8 \pm 8.3%.

<u>Discussion</u>. Crs can be safely, rapidly and reliably measured in the anesthetized infant or child who is spontaneously breathing via an anesthetic mask using a non-invasive method of volume recruitment as described. The correlation of Crs to height is similar to that described for Crs measured in young children who are anesthetized and paralysed, and ventilated via an endotracheal tube (Figure 1).

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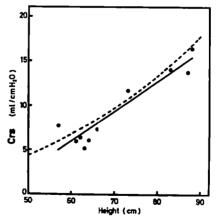


Figure 1. Correlation of Crs with height for the subjects of this study with the linear regression (solid line). This is compared with the summary equation of Sharp et al (1) for Crs vs. height in anesthetized, paralysed, intubated subjects (hatched line).

Title: LOWER ESOPHAGEAL CONTRACTILITY AND ASSESSMENT OF DEPTH OF ANESTHESIA DURING OPEN HEART SURGERY

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Introduction Despite recent advances in the anesthetic management of patients undergoing open heart surgery (OHS), little is known concerning the depth of anesthesia during various surgical stimuli. Presently, clinical, hemodynamic, electroencephalographic (EEG), or somatosensory evoked potential (SEP) measurements are used to monitor depth of anesthesia. Occasionally, awareness has been reported in patients without changes in these monitors. Recently, continuous monitoring of spontaneous and provoked lower esophageal contractility (SLEC and PLEC) has been shown to be useful for evaluating the depth of anesthesia. Tertiary esophageal contractions are stress related and their presence during anesthesia may indicate an inadequate depth. The present study was designed to (1) evaluate the depth of anesthesia during OHS and hypothermic cardiopulmonary bypass (CPB) utilizing high-dose fentanyl or isoflurane anesthetic techniques, and (2) compare LEC with other signs of anesthetic depth.

Methods With institutional approval and informed consent, measurements were performed on 22 patients for elective OHS. All subjects received a standard premedication of lorazepam, 2-4 mg, orally, and then were randomly assigned to one of two groups. Group A (N=11) received high-dose fentanyl (75-125 mcg/kg) and Group B (N=11) received an induction dose of thiamylal sodium, 2-4 mg/kg, I.V., and isoflurane (0.5-2.5% end-tidal concentration). A continuous infusion of atracurium was used for muscle relaxation. Both groups were ventilated with an F10 of 1.0, and the end-tidal CO was maintained at 40 mmHg. Standard hemodynamic monitoring for OHS was utilized. In addition, the EEG was monitored using frontal and parietal leads bilaterally and frequency (EEGF) was analyzed by spectral analysis. Median nerve SEPs were recorded over the brachial plexus and contralateral sensory cortex (N-19). The SEP latencies (SEPL) were corrected for temperature. The Neurotrac* spectral analyzer was used for monitoring both the EEG and SEPs. Following intubation, a disposable esophageal balloon-tipped probe for the continuous monitoring of SLEC and PLEC was inserted and the data was displayed and recorded by the Lectron 302.** Total LEC activity was calculated and displayed by the monitor as the esophageal contractility index (ECI); ECI = 70 x SLEC + PLEC. The ECI was compared with hemodynamic measurements (MAP, HR), EEGF and SEPL at: (I) postintubation; (II) sternotomy; (III) CPB cooling, esophageal temperature (ET) 32-28°C; (IV) CPB with ET < 25°C; (V) CPB - rewarming ET 28-32°C; (VI) post-CPB; (VII) sternal closure. The anesthesiologist was blinded to the EEG, SEP, and LEC monitoring, and anesthesia was administered using only clinical signs. Data was analyzed by chi-square analysis, Student's t-test, and analysis of variance; a p value of less than 0.05 was regarded as significant.

Results Groups A and B were not significantly different by hemodynamic, EEG, SEP, or LEC criteria; thus, only the combined data is shown in the Table. Of the 23 significant hemodynamic

episodes, 78% were accompanied by LEC and/or EEG or SEP changes. Of 33 EEG/SEP episodes, 45% were accompanied by LEC and/or hemodynamic changes, while only 35% of the 55 LEC episodes (ECI > 50) were accompanied by EEG, SEP, or hemodynamic changes. There were significantly more EEG, SEP, or LEC events than hemodynamic events. There were more episodes detected by LEC(ECI) than by any other parameter. Upon postoperative followup, no patients reported awareness during the operation.

Discussion The frequency and amplitude of lower esophageal contractions has been proposed as a correlate to anesthetic depth. During deep anesthesia there is little or no intrinsic esophageal activity, while during light anesthesia, LEC is evident. An increase in anesthetic dose, such as an additional dose of fentanyl or a change in the inspired concentration of volatile anesthetic, is sufficient to suppress LEC. LEC is not affected by skeletal muscle relaxants since the musculature of the lower half of the esophagus is nonstriated. The motor activity of the esophagus is predominantly controlled by brain stem nuclei and mediated by vagal pathways. It is assumed that the inhibitory effect of anesthesia upon LEC results from the central neurological effect of the anesthetic agents.

The present study revealed that 65% of increased LEC episodes and 55% of increased EEG/SEP combined episodes were not accompanied by changes in other parameters. Since 78% of hemodynamic changes, the traditional measure of anesthetic depth, were accompanied by LEC and/or EEG/SEP changes, it is doubtful that the data resulted from falsely positive signals. The data suggests that an inadequate depth of anesthesia during OHS may be more common than previously appreciated, and sophisticated cerebral or esophageal measurements may be able to detect it during OHS. * Interspec, Inc., Philadelphia, Pennsylvania ** American Antec Inc., Valencia, California

TABLE

nemodynamic, Cerebra	and LEC	epis	odes				
Stages	Ι	II	III	IV	V	VI	VII
MAP or HR# (>20%△)	5	8	0*@	0*@	0*@	3	7
EEG (> 20% △)	2	3	1	0*	1	5	8
SEP (> 20% A)	2	0	3	5*	1	1	1
SLEC (> 3/5min)	11	7	7	4	4	9	5
PLEC (> 30 mmHg)	9	0@	5	2*	2	8	3
ECI (> 50)	13	3 7	8	5	4	11	7

- * Mean value significantly changed from baseline # Significantly fewer overall episodes than other measures
- @ Significantly fewer episodes than observed at other events.

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Title: MEDIAN NERVE EVOKED POTENTIALS DO NOT PREDICT PNEUMOCEPHALUS IN THE SITTING POSITION

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Introduction. Pneumocephalus is a described complication of surgery in the seated position in the surgery where air enters through the surgical iteld and tracks forming an air pocket between the train and the most superior portion of the skull. Comatosensory evoked response (SSEP) monitoring as also been used during spine or neurosurgery in the sitting position to monitor neural pathways which may be at risk during the surgery. Two reorts (1,2) have noted alterations in the cortical implitude of the SSEP response with pneumocephalus, his is presumably due to the layer of air between the brain and recording electrodes on the scalb ausing a reduction in transmission of the geneated signal. We examined the correlation of this indirg with pneumocephalus in our patient population.

Methods. Twenty-one patients undergoing neurourgery for tumors in the posterior fossa particiated in this institutionally-approved study conucted between July 28, 1986 and February 25, 1987. postoperative computerized tomogram was conduced within three days postoperatively to evaluate he perioperative intracranial structures; pneumo-ephalus was documented by the appearance of postperative air which was not present preoperatively. During the surgical procedure brainstem audi-

During the surgical procedure brainstem audiory and somatosensory evoked responses were moniored and alterations in the amplitude or latency
oted. The median nerves were stimulated by steile subdermal needle electrodes unilaterally by
300 microsecond constant current square wave at
milliamps above the determined motor threshold
t 8.7 Hz. Responses were recorded by a Nicolet
struments CA-1000 signal averager using bandpass
iltration of 5-250 Hz and analysis window of 50
illiseconds. Averaged responses of 250 artifact
tee stimulations were recorded. For the purposes
this study, an alteration in the MN-SSEP was
maidered to be significant if the corticaly deived amplitude (NZO to P25) of either median
ever response decreased repeatedly to less than

erve response decreased repeatedly to less than % of its running baseline value or if the latence the either N2O peak increased in excess of 10% the running baseline value.

Anesthesia was conducted using Sodium thiopenal or midazolam induction followed by infusions the induction drug. Fentanyl or sufentanyl was ven as a bolus at induction and continued as fusion or intermittent small boluses. The paents were paralyzed with pancuronium and ventited with air and oxygen. Nitrous oxide was not sed during the procedure.

Chi-squared analysis was utilized to compare me occurrence of pneumocephalus and evoked resonse changes.

Results. Ten incidents of pneumocephalus were documented in these 29 patients. Seven patients had charges in the SSEP amplitude or latency. These results are tabulated in Table I.

Table 1
Occurrence of Pneumocephalus and SSEP Changes

SS	SEP	No Change	Change
Pneumocephalus Yes	3	3	7
No		11	0

Of the 10 cases of documented pneumocephalus, only seven had alterations in the MN-SSEP. No patients had MN-SSEP changes occur during the procedure without documented pneumocephalus, and three patients had pneumocephalus without MN-SSEP changes. The chi-square value for the data is 11.55 (p < 0.001).

<u>Discussion.</u> The loss of MN-SSEP evoked responses during a surgical procedure may signal a pathologic injury or ischemia to that portion of the nervous system which subserves the neural transmission of the evoked response. Other factors, such as anesthesia or technical factors may cause alterations which confuse the interpretation of potential neural injury. Pneumocephalus, which occurred in 10 of these 21 procedures is one of these interfering factors.

The knowledge that intracranial air has occurred is of value to consider alteration in the use of nitrous oxide during anesthesia, as well as for consideration in the differential diagnosis of slow awakening.

The failure of MN-SSEP to always predict pneumocephalus may represent differences in the quantity of air and the actual position of the patient (i.e., whether the air collected between the cortical generators and the electrode positions. Thus MN-SSEP responses do not always predict pneumocephalus. It is of interest, however, that all MN-SSEP charges in this study occurred in patients with pneumocephalus despite the possibility of SSEP charges from neural injury.

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Title: Authors: CORTICAL MOTOR EVOKED POTENTIALS PRODUCED BY MAGNETIC STIMULATION - INITIAL STUDY.

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Introduction. Current FDA-approved methods for intraoperative spinal cord monitoring are the wake-up test, the somatosensory evoked potential (SSEP) and the electrical motor evoked potential (MEP). However, each of these have potential disadvantages: the wake-up test involves the risk of inadvertent extubation and repeated induction of anesthesia, SSEP may remain unchanged after spinal cord injury (1) and electrical MEPs are too painful for preoperative assessment (2). Since the magnetically-induced MEP avoids these disadvantages, it is currently under investigation for intraoperative monitoring. As a necessary first step, we optimized stimulation sites and assessed the effects of magnetic cortical stimulation on mental status in the absence of anesthesia.

Methods. Twelve non-medicated, neurologically normal, adult volunteers were studied with IRB-approved informed consent. Mental status examinations were given before and after stimulation (3). Subjects were stimulated at 80% of maximum with a Cadwell MES-10 magnetic stimulator that was triggered by a Cadwell 7400 evoked potential monitor. The center of the 9 cm-coil was placed precisely over the stimulation site. Subjects were stimulated at approximately 1 s intervals at 8 cortical sites. Averaged EMG responses from triplicate stimulations were obtained from the tibialis anterior and the first dorsal interosseous muscles bilaterally. Using the International 10-20 electrode placement system as a reference, the sites were as follows: 1) 5% of the inion to nasion distance posterior to C_Z , 2) 5% posterior to the point midway between C_Z and C_Z , 3) 5% posterior to C_Z , 4) 5% posterior to C_A . Sites 5 through 8 were an additional 5% of the inion to nasion distance posterior to sites 1 through 4, respectively.

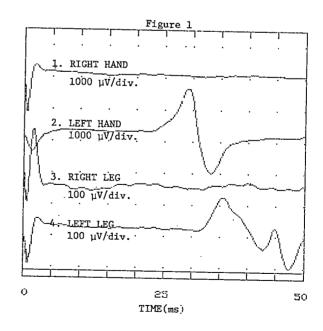
Results. Figure 1 shows a typical response obtained by stimulating site 4. Waveforms 1 and 3 represent the right arm and leg, respectively. Waveform 2 represents a typical left hand response, which is characterized by an N_1 wave with a mean latency of onset of 23.16 ± 1.32 (SD) ms and a mean amplitude of 1.43 \pm 1.09 mV and a P₁ wave with a mean latency of onset of 29.30 \pm 1.98 ms and a mean amplitude of 1.22 \pm 1.01 mV. Waveform 4 represents a typical left leg response which is characterized by an N_1 wave with a mean latency of onset of 31.85 \pm 2.04 ms and a mean amplitude of 0.19±0.14 mV. Stimulation at site 4 produced a contralateral hand and leg response in 10 of the 12 subjects, making it the most reliable. Central sites tended to stimulate the hands bilaterally and, in about half of the cases, a small bilateral leg response. The lateral sites tended to elicit a contralateral arm and leg response. No significant changes were noted between the mental status exams before and after the stimulation and no significant aftereffects were noted.

<u>Discussion</u>. This study showed that it is possible and safe to obtain an MEP from both the upper and lower extremities from a single magnetic stimulation site over the motor cortex. The largest percentage of usable response was produced at site 4.

Acknowledgements. 7400 Evoked Potential Monitor was provided by Cadwell Laboratories, Inc., 1021 North Kellogg Street, Kennewick, Washington 99336

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Title:

DOSE-RESPONSE RELATIONSHIPS CF EDROPHONIUM AND NEOSTIGMINE AS ANTAGONISTS OF

DEEP AND MODERATE ATRACURIUM BLOCKADE.

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Introduction. The effect of reversal agents depends on the degree of spontaneous recovery when they are injected (1,2). It has been suggested that neostigmine is a better antagonist of profound blockade than adrophonium (2,3). The purpose of this study was to determine dose-response relationships and potency ratios for edrophonium and neostigmine as antagonists of deep (99%) or moderate (90%) atracurium blockade.

Methods. The protocol was approved by the Hospital Ethics Committee. Eighty ASA status I and II adults undergoing elective surgical procedures were studied. Anesthesia was induced with thiopental 3-5 mg/kg and maintained with N20 70% in 02 and enflurane 0.5-1.0% end-tidal. Evoked force of contraction of the adductor pollicis was neasured using train-of-four stimulation every 12 seconds. Atracurium 0.4 mg/kg was administered and enflurane concentrations vere maintained constant. Patients were candomly assigned to receive neostigmine (.005, .01, .02 or .05 mg/kg) or edrophonium (.1, .2, .4 or 1 mg/kg) at either 1% (deep), or 10% (moderate) spontaneous recovery of first twitch height (T1) relative to control. Linear regressions were obtained between the logit transformation of Il recovery and log dose for each minute up to 15 minutes following the administration of the antagonist. The doses expected to produce 80% recovery (ED80) of Tl with moderate and deep blockade were compared sing Student's t test. Results are expresed as mean + SEM, and a P value < 0.05 as considered significant.

Results. At 7 and 10 minutes after idministration of the reversal agent, significantly more neostigmine and edrophonium as required for 80% T1 recovery from deep versus moderate atracurium blockade. Figure). Compared with moderate blockade, leep blockade required 1.5-3 times as much leostigmine and 4-8 times as much edrophonium to achieve the same degree of twitch ecovery. Edrophonium was relatively less effective against deep blockade. Potency atio (ED80 edrophonium/ED80 neostigmine) to 10 min was significantly greater with leep (35.4 + 8.9) than moderate (16.6 + 1.2) blockade (p < 0.025).

Discussion. The study demonstrated that the dose-response relationships for edro-honium and neostigmine as antagonists of tracurium blockade depends critically on the degree of spontaneous recovery. This is especially true of edrophonium, whose otency, compared with that of neostigmine, ecreases markedly when used to reverse eep blockade. Thus, neostigmine may be

superior to edrophonium as an antagonist of deep atracurium blockade.

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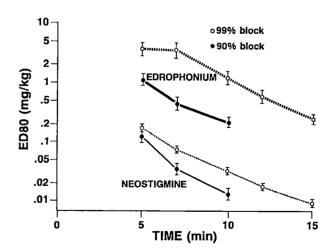


Figure. First twitch height ED80 of neostigmine (bottom) and edrophonium (top) as antagonists of moderate (90%) or deep (99%) blockade. Bars represent SEM.

Title: "PRIMING" WITH NEOSTIGMINE: FAILURE TO ACCELERATE REVERSAL OF SINGLE TWITCH

AND TRAIN-OF-FOUR RESPONSES.

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Introduction. Giving neostigmine in divided doses (priming) may accelerate reversal of atracurium blockade, using trainof-four stimulation (1). However, TOF is associated with a more rapid onset of neuromuscular blockade than single twitch (ST) (2). This study was designed to determine whether TOF also accelerated the apparent onset of action of neostigmine, and whether the "priming" effect could be a consequence of the mode of stimulation used.

The protocol was approved by the Hospital Ethics Committee. Fourteen adult patients undergoing elective surgical procedures and who gave informed consent were studied. Anesthesia was induced with thiopental 3-5 mg/kg, and maintained with nitrous oxide 70% and enflurane 0.5-1.0% end-tidal. The enflurane concentration was maintained constant in each patient. The ulnar nerves of both elbows were stimulated using train-of-four (TOF) every 12 s, and the evoked force of contraction of both adductor pollicis muscles was measured. Atracurium 0.5 mg/kg was administered. When first twitch height (Tl) in either adductor pollicis recovered spontaneously to 1% of control, one arm was selected at random to receive single twitch (ST) stimulation, while TOF stimulation continued to be delivered to the other arm. When the mean T1 of both adductor pollicis had recovered to 10% control, patients were randomly assigned to receive neostigmine 0.04 mg/kg administered as a single bolus or as a divided dose (initial dose = 0.01 mg/kg, followed 3 minutes later by 0.03 mg/kg). Recovery of Tl obtained by TOF was compared with ST using Student's paired t test. The effects of single and divided doses of neostigmine were compared using unpaired Student's t test. Results are expressed as mean + SEM. A P value < 0.05 was considered significant.

Results. There was no statistically significant difference between the height of the first twitch on train-of-four and single twitch height (Figure). Compared with single doses, administration of neostigmine in divided doses (priming) resulted in an initially slower recovery of Tl. However, no differences were observed at 10 min (Figure). At 5 min, TOF ratio was 53 + 4% and 28 + 3 min for single and divided doses respectively (p<.001). At 10 min, it was 72 + 2 and 65 + 5 respectively (N.S.).

Discussion. This study demonstrated that the time courses of neuromuscular blockade reversal measured by TOF and ST were very similar. This is in contrast to the marked acceleration of atracurium onset

time associated with TOF stimulation, which was attributed to the muscle contraction—induced increase in blood flow (2). In the present study, blood flow increases were negligible because of the profound neuro—muscular blockade at the time neostigmine was injected. When neostigmine was administered in divided doses (priming), a significant slowing, instead of an acceleration, of reversal was observed. The reasons for the discrepancy between this study and a previous one (2) are uncertain. It is concluded that (1) the effect of neostigmine can be measured with either ST or TOF, and (2) "priming" with neostigmine does not appear to be effective.

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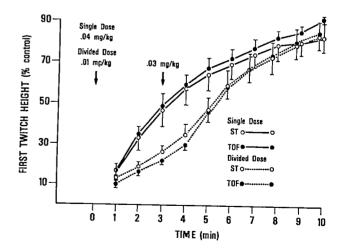


Figure. First twitch height in train-offour (TOF) or single twitch height (ST), with neostigmine given in single or divided doses, versus time after first administration of neostigmine.

Title: A COMPARISON OF DERIVED PARAMETERS USED IN ELECTROENCEPHALOGRAPHY

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Introduction. Various techniques and devices are available to assist clinicians in assessing a patient's depth of anesthesia. Many investigators have looked into the effects of different anesthetic agents on the electrical activity of the brain (EEG). The classical clinical signs of anesthetic depth¹ - blood pressure, heart rate, pupil dilation_respiration, etc. can be obfuscated with today's modern anesthetic drugs and techniques. Several studies² ³ have shown that monitoring the EEG can indicate CNS status and could enhance depth assessment for most general anesthetic techniques.

The problem with monitoring the EEG is that at best it is difficult to interpret. In trying to simplify this task, several derived parameters have been proposed, using different techniques of waveform analysis. Puritan-Bennett's ABM-2 monitor uses zero-crossing frequency (ZXF), and average amplitude. Neurometric's Lifescan monitor uses an algorithm to calculate the "activity edge frequency (AEF), which tracks the upper limit of frequency content in the EEG signal, similar to spectral edge frequency. This study assesses the relationship between normal sleep EEG and anesthetic sleep EEG using these two different waveform analysis techniques.

Methods. Six adult patients scheduled for elective surgery with general anesthesia were studied. Four adult subjects were studied for normal sleep data. All of the subjects had electrodes placed on the lateral edge of the frontalis muscle and on the posterior auricular muscle. A ground reference electrode was placed over the middle of the frontalis muscle.

The recorded EEG signal was input to both the ABM-2 and the Lifescan EEG monitors. The processed output data was collected on a DEC/MINC computer and averaged to obtain the low, average, and high AEF and amplitude values for each of the periods of time considered. The data was collected during deep anesthesia for the intra-operative subjects. Four standard stages were assessed for each of the normal sleep subjects by visual inspection of raw waveforms. These stages are: stage 1 (transitional), stage 2 (first sleep stage), delta sleep (deep non-REM sleep), and REM (dream sleep).

Results and Discussion. The statistical means and standard deviations of the data are shown in tables 1-4. The data points out the significant differences in the two waveform analysis techniques. An examination of the EEG raw waveforms shows significant difference between deep anesthesia and all four normal sleep stages as shown in figure 1. The ABM-2 ZXF seems more sensitive to EEG signal frequency variance, because more of the EEG signal content is at the lower frequencies. The Lifescan monitor has a wider range of frequencies for the same data. The Lifescan seems more sensitive to EEG signal amplitude variance. For the comparison of the normal sleep stages to deep anesthesia, deep anesthesia had a significantly larger difference in

the frequency value for the ABM-2 than did the Lifescan. The Lifescan monitor had a larger difference in the value of amplitude during deep anesthesia than during the four sleep stages. In general, the visually apparent differences in EEG raw waveforms were not reflected by significant differences in the derived parameters of either device.

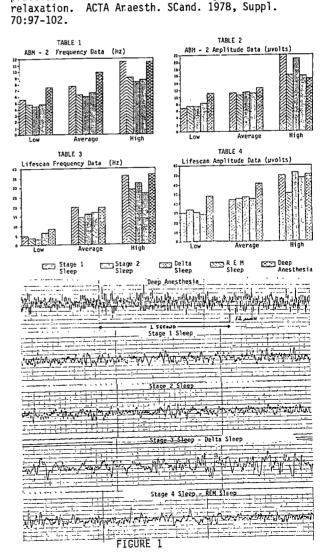
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Title: SUFENTANIL PLUS LOW-DOSE KETAMINE, THE IDEAL INDUCTION MIXTURE?

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 $\underline{\text{Introduction}}$: Ketamine is a safe, rapidly acting parenteral anesthetic and analgesic which in many ways comes close to satisfying the criteria for an ideal intravenous anesthetic. However, significant drawbacks are a possibly dose-related incidence of unpleasant emergence reactions in 5-30% of patients, and a transient dose-related rise in rate-pressure product and cardiac index (1). Sufentanil is a synthetic ultra-potent opioid analgesic which, in high doses, produces amnesia and loss of consciousness (2). In more moderate doses as part of a balanced anesthetic, it provides hemodynamic and autonomic stability. Truncal rigidity and respiratory depression seem to be the major side effects (2). We hypothesize that low dose ketamine combined with low to moderate dose sufentanil will: (a) provide amnesia and loss of consciousness for laryngoscopy and endotracheal intubation; (b) provide, as part of a routine balanced anesthetic, profound analgesia similar to a sleep dose of narcotic but without significant postoperative respiratory depression; (c) by combining sufentanil and ketamine, totally prevent emergence phenomena while maintaining cardiovascular stability.

Methods. With institutional ethics committee approval, 30 ASA I or II adults, age 18-60, were randomized in a double-blind fashion to one of three different induction techniques. Group I received 0.1 $\mu g/kg$ sufentanil, followed 3 mins later by 0.3-0.6 mg/kg ketamine. Group 2 received 0.5 $\mu g/kg$ sufentanil, followed 3 mins later by 0.3-0.6 mg/kg ketamine. Group 3, control, received saline followed by pentothal, 4-5 mg/kg. One minute following loss of consciousness, all patients received 1.5 mg/ kg succinylcholine and intubation was performed one minute later. IPPV was instituted and anesthesia was maintained with 60% N2O in O2, vecuronium and isoflurane as required to maintain heart rate (HR) and mean arterial pressure (MAP) within ± 20% of baseline. HR and MAP were recorded at induction, 2, 4, 6, 9, and 14 mins, and at 5 min intervals thereafter. Objective (by an investigator unaware of anesthetic technique) and subjective linear analogue pain scores were obtained in the recovery room, and patients filled out a questionnaire at 24 hrs postoperatively.

Results. There were no significant differences between groups for age, height, weight, ASA classification, duration of laryngoscopy, duration of surgery, or type of surgery (p<0.05).

End-tidal CO₂ concentrations were not significantly different following pre-treatment with either dose of sufentanil (Group 1, 4.29% \pm 1.03; Group 2, 3.56% \pm 2.15) compared to saline (Group 3, 4.14% \pm 0.85) (p<0.05). No patient in Group 1 required supplementation with pentothal to achieve unconsciousness; however, 3 patients in Group 2 required pentothal supplementation; all patients in Group 3 lost consciousness with the single 4-5 mg/kg dose of pentothal. Mean ketamine dose in Group 1 was 0.36 mg/kg (\pm 0.126), and in Group 2, 0.48 mg/kg (\pm 0.155).

The incidences of rigidity were not different between the three groups (p<0.05).

HR and MAP rose significantly higher from baseline immediately following intubation, and 2 mins later in Group 3 (control) compared to Group 1 (see Tables 1 and 2).

Postoperatively, the incidences of nausea, vomiting and dreaming were not significantly different between the three groups (p<0.05). There were no incidences of awareness.

Objective pain scores at 30 mins postoperatively were significantly lower in Group 1 (2.61 \pm 1.57) compared to Group 3 (4.34 \pm 1.25), (p<0.05), though at 60 and 90 mins postoperatively no differences were noted. No significant differences between subjective pain scores were noted at any time (p<0.05).

There was no difference in the incidence of bradypnea (RR \leq 12) between the three groups (p<0.05).

<u>Discussion</u>. The combination of low to moderate dose sufentanil followed by low dose ketamine seems to provide many of the advantages of each agent while minimizing their disadvantages. In particular, lug/kg sufentanil, followed by 0.3-0.6 mg/kg ketamine seems to provide amnesia and unconsciousness, stable hemodynamics during intubation, and superior early postoperative analgesia compared to pentothal. These advantages do not seem to be accompanied by an increased incidence of preinduction rigidity or postoperative nausea, vomiting or respiratory depression.

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TABLE 1
INCREASE IN MEAN ARTERIAL PRESSURE

		Immediately after intubation	2 mins after intubation
Group Group	2	* 7.5 ± 13.5 mmHg 12.4 ± 07.6 mmHg	* 0.4 ± 15.2 mmHg 14.0 ± 14.6 mmHg
Group	3	26.3 ± 22.2 mmHg	$24.2 \pm 17.8 \text{ mmHg}$

^{*} Group 1 significantly different from Group 3 (p < 0.05).

TABLE 2 INCREASE IN HEART RATE

	Immediately after intubation	2 mins after intubation	
Group 1	* 9.1 ± 16.6	*0.7 ± 12.7	
Group 2	19.2 ± 11.3	17.8 ± 17.7	
Group 3	29.7 ± 13.6	25.1 ± 12.8	

^{*} Group 1 significantly different from Group 3 (p<0.05).

Title: EVALUATION OF THE REFLECTANCE PHOTOMETER (GLUCOMETER II) FOR INTRAOPERATIVE BLOOD GLUCOSE

DETERMINATION

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Introduction. The ability to determine serun glucose values accurately and quickly during surger; is essential for patient safety. Presently, intraoperative glucose analysis is performed in hospital laboratories that utilize glucose oxidase methodology. Although reliable, this method is costly in terms of money, time and personnel. Reflectance photometers quantitate the color developed during a series of chemical reactions when whole blood is placed on a reagent stick. This technology has been successfully employed by diabetics for selfmonitoring of insulin therapy, but has never been evaluated for intraoperative use. This study investigated the suitability of employing the Glucometer II Blood Glucose Meter (Ames Division; Miles Laboratories, Elkhart, Indiana) during surgery.

Methods. The study population consisted of 93 patients undergoing surgery who required arteria catheters and intraoperative serum glucose determinations. The age of the subjects ranged from three months to 92 years. The investigation was approved by the Committee for the Protection of Human Subjects of the Medical School. Within five minutes after a heparinized arterial specimen was drawn for laboratory glucose determination employing the Astra IV (Beckman, Puerto Rico), whole blood glucose values were measured from a capillary, as well as arterial, sample using the Glucometer II Individuals using the Glucometer II were properly trained and exhibited a level of proficiency established by the Ames Division. Data was analyzed by least square linear regression analysis correlation coefficient and standard error.

Results. Overall, a highly significant linear association was observed between capillary and arterial values determined by the reflectance photometer and that obtained by the glucose oxidase method, Figs 1 and 2 respectively. There was a general trend towards greater absolute and percentage deviation with higher serum glucose values over 200mg/dl. The coefficient of variation for the Glucometer II was 4.82% at 151 mg/dl (n = 10) and 8.84% at 96mg/dl (n = 10). The range of blood glucoses observed was 83-313mg/dl, 5% less than 90mg/dl and 8% greater than 250mg/dl.

Discussion. The hospital laboratory values were approximately 11% higher than the Glucometer II. These results are consistent with the fact that serum or plasma values are about 10-15% higher that those of whole blood (1). The accuracy of reflectance photometers such as the Glucometer II is highly dependent on the skill of the user and quality control of testing procedures and equipment. The visual interpretation of test strips without a meter may be accurate to only ±30-40% of values obtained from more standard methods and are too inaccurate to be of practical clinical benefit over the range of blood glucose commonly encountered in the operating room. In conclusion, intraoperative use of a reflectance photometer such as the Glucometer II

will afford the anesthesiologist with accurate and readily available glucose determinations. The Glucometer II is light-weight, compact, convenient to use and easily transportable, taking only 50 seconds for each test.

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FIGURE I

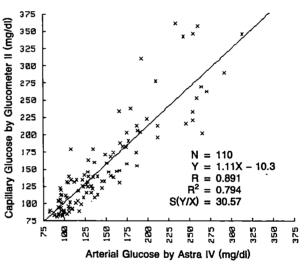
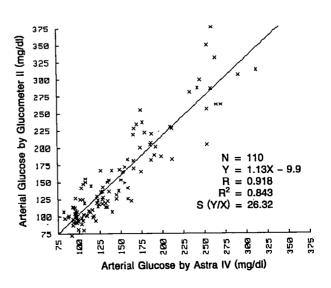


FIGURE II



Title: ROUTINE MONITORING OF NEUROMUSCULAR FUNCTION

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Introduction. The rational and optimal use of the shorter acting non-depolarizing muscle relaxants, vecuronium and atracurium, necessitates routine monitoring of their neuromuscular effects. This investigation evaluated a simple method which can replace the widely used visual and tactile evaluation of the train of four (T4) responses by providing the anesthesiologist with a graphic display of the T4 responses on any standard blood pressure (BP) monitor screen. The anesthesiologist's assessment of the degree of neuromuscular blockade (NMB) based on the displayed T4 responses, was compared with the simultaneously recorded mechanical measurements.

Method. Eighty healthy adult patients of both sexes with a mean age of 44 and mean weight of 68 kg undergoing elective outpatient procedures were randomly assigned to 2 groups of forty. Institutional Review Board approval was secured and informed consent was obtained from all patients. Anesthesia was induced with sodium thiopenthal 2-3 mg/kg and maintained with a 4:2 L/min N₂0-O₂ mixture supplemented with incremental doses of Fentanyl 0.005 mg/kg. The priming dose of 0.01 mg/kg vecuronium or 0.05 mg/kg atracurium was given 5 min prior to the intubating dose of 0.1 mg/kg vecuronium or 0.5 mg/kg atracurium. Ventilation was controlled. Supplemental doses of vecuronium 0.02 mg/kg or atracurium 0.08 mg/kg were given as required to maintain 80-90% NMB. When spontaneous recovery of neuromuscular function (NMF) was not complete at the end of surgery (T4 ratio < 0.8), the residual block was antagonized with edrophonium 0.5 mg/kg combined with atropine 0.008 mg/kg. The NMF was measured by both recording and displaying the force of thumb adduction evoked by supramaximal stimulation of the ulnar nerve at the wrist. An adductor pollicis monitor (1,2), modified for routine clinical application was used. A constant resting tension of 400-600 g was applied. The ulnar ${\tt nerve\ was\ stimulated\ with\ a\ pair\ of\ noninvasive\ skin}$ electrodes using a Neuro Technology constant current battery powered portable peripheral nerve stimulator with current output of 80 mA. The T4 stimuli were applied as square pulses of 0.2 msec duration at 0.5 sec intervals and repeated every 10 sec. The output from the force transducer was displayed and recorded on a Datascope 2000 monitor. During each study, while observing the displayed T4 responses on the screen, the anesthesiologist reported the time and his assessment of the T4 ratio and the number of twitches in the T4 responses.

Results. Twenty four pairs (assessment of screen display vs measurement of mechanical recording) were selected from each study for the statistical evaluation. Eight pairs were selected from the onset, eight during the block and eight

during spontaneous or induced recovery. No statistically significant differences were found between the data obtained from clinical assessment of the displayed T4 responses and recorded mechanical responses. The evoked T4 responses of the adductor pollicis muscle recorded during each study were quantitated as follows: peak tension of the first twitch in the T4, the number of twitches in the T4 and the ratio of T4/T1. The amplitude of the first twitch in the T4 was compared to that of the control T4 prior relaxant administration. Clinically, the degree of NMB was estimated from the number of twitches in the T4; one response considered to correspond to 90%, two responses to 80% and three responses to 70% NMB (3,4). When all four twitches were present, the T4 ratio was estimated. A typical example of the anesthesiologist's report for the time base on the screen at 10:00 A.M. included the number of twitches in T4, the T4 ratio and the percentage of NMF. This was reported as follows: Time 10:05:02; two twitches; ratio 0; block 80.

Discussion. Monitoring of NMF is important when shorter acting relaxants are used. Currently the visual or tactile observation of muscle responses to peripheral nerve stimulation is the most commonly used clinical technique. This method is highly subjective. Various monitoring devices have been introduced for evaluation of NMF but several drawbacks prevented their widespread use. These include the need for additional sophisticated equipment, calibration procedures, the set-up time and the cost. This study shows that the display of T4 responses on the BP monitor screen is a reliable method of neuromuscular function monitoring. It is simple to learn and accurate in assessment of the degree of NMB and its recovery. This method also provides the anesthesiologist with the advantage of simultaneous assessment of NMF, EKG and BP on the same screen display. His concentration is not detracted to different areas of observation. This method is highly suitable for routine clinical monitoring in the operating room and recovery room.

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Title: INITIAL EXPERIENCES OF THE NATIONAL COMMITTEE FOR ANESTHESIOLOGY REVIEW

Authors:

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Introduction. Increasing numbers nesthesia-related lawsuits and serious concerns bout the quality of anesthesia care has focused attention on anesthesiology-related ational edicolegal issues. Careful evaluation of ndividual malpractice cases by a national nesthesiology committee with input from academic nd private practice anesthesiologists, although otentially valuable, was not available until the ormation of the National Committee for nesthesiology Review (NCAR) in 1981. This report escribes the components and functions of NCAR and ummarizes the results of its first onsultations.

Components, Functions, and Ideals. NCAR aintains the philosophy that the analysis of any Components, edicolegal problem should be unbiased in terms of efending or finding fault with medical practice, echnique, or equipment without regard to whether he consultation was solicited by plaintiff, efendant, or any other person or institution. CAR renders its opinion about the appropriateness of anesthesia care through the preparation of a ritten report of "composite review." Forty rell-qualified diplomates of American Board of mesthesiology from various institutions and rivate practice throughout the United States serve is the NCAR Editorial (Review) Board. Each alpractice case submitted to NCAR is reviewed by our or five members of the editorial board. The ditor-in-chief selects those editorial board nembers who are to review a particular case based in the following criteria: 1) At least one should me a recognized authority in the area of anesthesia n question. 2) One reviewer should not be articularly noted for expertise in the area in juestion. 3) One reviewer should practice in a ion-university hospital. 4) The reviewers should represent different geographical areas. These eviewers perform an in-depth analysis of the ledical records, depositions, etc., and submit their report the NCAR editor-in-chief who in turn from a consensus analysis from the review submitted and forwards this "composite review" to the requesting attorney. Soliciting parties have requested a "one reviewer" verbal or written

eport, however, this service was discontinued.

NCAR does not provide "expert witness" reveal the identity of the reviewers providing input to the composite report. However, after the composite review is completed and sent to the soliciting party, when requested, the editor-in-chief will contact the editorial board members in question and inquire whether they have iny desire to be further involved with the case or its principals. If they co, their names/addresses are revealed to the soliciting party. The reviewer

then acts as a consultant or expert witness outside of his relationship with NCAR but may $\,$ utilize the composite review or any individual review as he/she considers advisable.

Results. A questionnaire was prepared and sent to the first thirty attorneys who requested NCAR reviews. Twenty-four of twenty-eight attorneys (two reviews were cancelled) requesting reviews responded to our survey. Nearly 80% of the initial survey respondents were attorneys for the plaintiff. An anesthesia equipment manufacturer, a pharmaceutical firm, and three anesthesiologists were defendants malpractice problems reviewed. One review was solicited by a hospital medical board requesting an evaluation of the anesthetic techniques used by an anesthesiologist working in its hospital. Eighteen to twenty-four cases have thus far been resolved with six remaining active. All of the six active cases have gone to trial. NCAR played a 49% role in the disposition of those cases which have been resolved. An average of twelve months elapsed from the time of the requesting party's receipt of the NCAR report until case disposition. In thirteen of twenty-three cases, the NCAR consensus was opposite to the interest of the party requesting the review. In twenty-three of twenty-four cases, the NCAR report was considered valuable, and in five cases, additional assistance in the form of depositions or expert witnesses were provided. The average settlement in those cases reviewed by NCAR was approximately \$1.2M with NCAR considered instrumental in assigning the amount of monetary compensation in nine of sixteen cases. Twenty-three of the twenty-four attorneys who requested NCAR reviews and responded to our survey indicated that they would use NCAR again.

Discussion. Analysis of twenty-four medicolegal problem cases reviewed by NCAR indicates that attorneys representing plaintiffs utilize the committee approx. 3.5 times as frequently as attorneys representing defendants. of those defense attorneys requesting NCAR reviews, 60% received reports which were considered unfavorable to their clients' cases, while 60% of plaintiffs' attorneys considered the NCAR report to be favorable or neutral. Despite the large number of reports unfavorable to their clients' cases, both plaintiff and defense attorneys were nearly unanimous in their assertion that the NCAR report was a valuable tool for use in case disposition and that they would indeed consult NCAR again should the need arise. These data suggest that reviews of anesthesiology-related malpractice cases by recognized authorities are valuable to and highly regarded by representatives of both sides of the

anesthesia medical liability issue.

Title:

COMPARISON OF CARDIOVASCULAR EFFECTS OF PIPECURONIUM VS.VECURONIUM IN PATIENTS FOR CORONARY

SURGERY

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Introduction. Pipecuronium bromide, (PIP) a recently developed nondepolarizing neuromuscular blocking drug, has chemical and pharmacological properties similar to pancuronium, but is reported to have minimal cardiovascular side effects. (1) In that aspect it is claimed to be similar to vecuronium (VEC) which is associated with the most stable hemodynamic course when combined with narcotic-O2 anesthesia in patients scheduled for CABG.(2) The present study examines and compares the cardiovascular effects of the two muscle relaxants in pts. scheduled for CABG

with narcotic-O₂ anesthesia.

Method. With their informed consent, 83 pts.
scheduled for CABG surgery were randomized to receive either PIP or VEC in conjunction with sufentanyl-02 anesthesia. Excluded from the study were those clinically unstable, elderly (>70), with liver, renal, or valvular heart disease, and females of child-bearing age. Premedication was morphine sulfate 0.1 mg/kg IM, scopolamine 0.4 mg IM and dermal NTG. Beta and calcium entry blocking drugs were continued through the morning of surgery. Pts. were induced with sufentanyl 6 mcg/kg, 100% O₂ and neuromuscular blocker (PIP:0.1 mg/kg or VEC:0.12 mg/kg) administered within 2 minutes. Hemodynamics were measured preinduction (baseline), 3 and 6 minutes post induction and 3 and 6 minutes post-intubation. was analyzed by an analysis of variance (repeatd measures) for differences between the two study groups at each measurement time and within each drug group at different measurement times, with P<0.005 as significant.

Results. There were no differences between groups regarding pre-op characteristics and baseline hemodynamics. Cardiovascular responses are summarized in Tables 1 and 2. Table 3 summarizes the number of patients who required drug interventions to maintain BP within 30% baseline or HR > 40.

<u>Discussion.</u> This study demonstrates both PIP and VEC when combined with sufentanyl-O₂ anesthesia provide similar and minimal changes in hemodynamics of patients scheduled for CABG. The number of interventions required to maintain BP and HR are increased due to our strict adherence to a clinical protocol. Related was

	Baseline	3 Min Post Relaxant	6 Min Post Relaxant	3 Min Post Intubation	6 Min Post Intubation
HR	65.1+/- 1.7	62.9+/- 2.2	64.3+/- 2.2	64.8+/- 2.4	62.2+/- 2.2
MAP	91.7+/- 1.7	82.4+/- 2.5	88.4+/- 2.6	90.4+/- 2.4	87.2+/- 2.5
CI	2.53+/- 0.08	2.33+/-0.09	2.60+/- 0.13	2.73+/- 0.14	2.56+/- 0.13
CVP	9.0+/-0.5	11 1+/- 0.5	11.3+/- 0.5	10.8±/- 0.4	10.0+/-0.4

13.1+/- 0.7

166+/- 12

1310+/- 49

13.2+/- 0.6

152+/- 9

1333+/- 60

12.7+/- 0.6

154+/- 8

1344+/- 57

12.8+/- 0.7

159+/-8

1329+/- 44

HEMODYNAMIC MEASUREMENTS WITH PIPECURONIUM

TABLE 1

PAWP

PVR

SVR

11.4+/- 0.7

182+/- 13

1435+/- 53

the use of a potent narcotic in relatively large anesthetic doses which can cause slowing of the heart rate when combined with muscle relaxants that have small influence on hemodynamics. Therefore, the hemodynamic response expected would be that of the narcotic administered in anesthetic dosages. Because PIP is more potent and has a longer duration of action than VEC (3) plus similar lack of influence on hemodynamics (1) PIP may be particularly suited for patients scheduled for CABG surgery.

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TABLE 2	HEMODYNAMIC MEASUREMENTS WITH VECURONIUM

HR	68.3+/- 2.2	69.8+/- 2.7	69.1+/- 2.5	68.4+/- 2.8	64.0+/- 2.3
MAP	94.6+/- 2	91.2+/- 3.2	93.7+/- 2.5	94.7+/- 2.3	93.1+/- 2.2
CI	2.7+/- 0.11	2.61+/- 0.12	2.78+/- 0.13	2.89+/- 0.15	2.61+/- 0.12
CVP	9.0+/- 0.7	11.5+/- 0.7	10.9+/- 0.5	10.3+/5	10.3+/- 0.5
PAWP	12.7+/- 0.8	12.6+/- 0.8	13.2+/- 0.8	12.7+/- 0.8	12.2+/- 0.8
PVR	155-/- 14	159+/- 15	125+/- 11	128+/- 8	138+/- 9
SVR	1386+/- 66	1306+/- 58	1298+?- 51 [:] '	1298+/- 64	1380+/- 58

TABLE 3	DRUG INTERVENT	ONS
	PIP	VEC
Neosynephrine Alone	5	2
Neo + Atropine/Robinul	1	1
Robinul Alone	2	3
Nitroglycerine Alone	4	3
Total Interventions	12/43	9/40
% of Group	27.9	22.5

There is no significant difference

ANESTH ANALG 1988;67:S1-S266

Title: THE INCIDENCE OF POSTOPERATIVE NAUSE AND VOMITING

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Introduction. The incidence of postoperative nausea (N) and vomiting (V) has most often been examined utilizing retrospective chart review. This one year prospective study was undertaken to identify factors influencing H and V and to determine if a discrepancy exists between N and V recalled (R) by patients and that documented (L) in nurses notes.

Methods. Adult (18 years) inpatients not requiring admission to an ICU were interviewed postoperatively and their charts reviewed. Eighty-two percent of the 1551 patients, (820 female (F) and 731 male (M)) were interviewed within 24 hours of surgery and the remainder Surgical procedures were later in their hospital stay. Surgical procedures were categorized as: intraoral (IR), intraoranial (IC), thoracis abdomina (IT), spine (SP), intraperitoneal (IP), extraperitoneal (EP), laparoscopy (LP) and superficial (SF. Patients were divided into 8 groups based on anesthetic technique used: Groups I, III, and V received enflurane (E), isoflurane (I), or halothane (H), respectively, and no narcotics intraoperatively (O). Groups II, IV and VI received a narcotic (N) in addition to the volatile agent. Groups VII and VIII did not receive a volatile agent (X; Group VIII received a narcotic. All patients also received nitrous oxide. Patients who received drugs with antiemetic properties (droperidol, scopolamine, hydroxyzine and promethazine) were excluded from analysis. Student's ttest for unpaired samples and the chi-square test were applied where appropriate.

Results. Only 52.5% of reported N and 62.5% of reported V were documented. The incidence of N and V was not associated with preoperative or intraoperative narcotic administration. The R incidence of N differed significantly between females (37.1%) and males (21.0%) (p < .001) as did V (25.7% and 14.5%) (p < .001). There was no significant difference in weight between those who reported N (mean 73.0 kg) and those who did not (73.5 kg), or V (72.6 kg and 73.6 kg). Patients who reported N were younger (mean age 39.5 years) than those who did not (43.9 years) (p < .001). Those who reported V were also younger (40.0 years) than those who did not (43.3 years), (p < .01. Superficial and intraperitoneal procedures, which comprised 85% of the total (Table 1), were associated with a similar incidence of N (30.2% and 30.7%), but the incidence of V was significantly greater in the SF group (23.2%) than the IP group (15.9%), (p < .01). The duration

of anesthesia in those who experienced N (mean 2.5 hr) and those who did not (2.6 hr) was similar. The same was true for V (2.5 hr and 2.7 hr). Patients who received I reported less N (25.4%) than those who received E (30.3%) or H (29.3%), but these differences were not statistically significant. The incidence of V was also similar with the three agents: (I = 19.3%, E = 20.5%, H = 20.9%). (Table 2).

Discussion. The interview technique demonstrated that the patient's perception of N and V varied significantly from the incidence documented in the chart. Studies citing postoperative N and V should be reviewed with this in mind. Gender and age were the only identifiable factors associated with N and V. The incidence of N was the same with superficial and intraperitoneal procedures but V was greater in the former group. The patient's weight, pre- and intraoperative narcotic administration, and volatile anesthetic agents employed were not predictive of postoperative N and V.

	Tab]	le 1		
Site	N	Naus	ea (%)	Vomiting (%)
		\mathbf{R}	D	R D
IR	27	25.9	20.7	22.2 17.2
IC	15	26.6	0.0	6.7 0.0
IT	15	6.7	6.3	0.0 6.3
SP	103	20.4	14.3	16.5 13.3
IP	404	30.7	17.3	15.9 11.6
EP	50	34.0	26.9	22.0 21.2
LP	10	40.0	20.0	30.0 20.0
SF	927	30.2	18.4	23.2 16.0
TOTAL	$1\overline{551}$	$\overline{29.5}$	$\overline{17.9}$	20.4 14.6
		_		
		le 2	(01)	(0/)
Agent	N		sea_(%)	Vomiting (%)
		R	D	R D
I (EO)	640	30.6	17.5	19.7 14.7
П (EN)	411	29.7	20.0	21.7 15.4
III (IO)	127	23.6	15.4	18.9 13.9
IV (IN)	117	27.4	12.6	19.7 11.8
V (HO)	136	30.9	18.1	22.1 15.1
VI (HN)	55	25.5	19.6	18.2 16.1
VII (XO)	17	29.4	11.8	17.7 0.0
VIII (XN)	48	35.4	22.0	25.0 18.0
TOTAL	$15\overline{51}$	29.5	$\overline{17.9}$	20.4 14.6

Title: CIMETIDINE AND SUCCINYLCHOLINE: POTENTIAL INTERACTION AND EFFECT ON NEUROMUSCULAR

BLOCKADE IN MAN

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Introduction. Cimetidine, an H₂ histamine antagonist, is the most frequently prescribed drug in the U.S., and is also routinely employed as an anesthetic premedicant. Cimetidine is known to decrease liver blood flow (1) and inhibit microsomal drug metabolism (2). A recent study demonstrated in vitro inhibition of pseudocholinesterase activity by H₂ antagonists (3). Since succinylcholine is metabolized by pseudocholinesterase formed in the liver, a potential exists for interaction between cimetidine and succinylcholine. This prospective study was designed to determine the effect of cimetidine premedication on the onset and duration of succinylcholine-induced neuromuscular blockade in man.

Methods. The study protocol was approved by the institution's Human Investigation Committee, and written informed consent was obtained from all patients. The subjects were 20 adult patients, ASA physical status 1 or 2. The patients were randomly allocated into two groups of 10 each. Group 1 patients received cimetidine 400 mg P.O. at bedtime and 400 mg P.O. 90 min prior to induction of general anesthesia. Group 2 patients acted as controls and did not receive cimetidine. No other premedication was given. After placement of a blood pressure cuff and EKG electrodes, anesthesia was induced with thiopental 4-6 mg/kg IV and maintained with fentanyl 3-5 μ g/kg and N₂O, 67% in O₂. Neuromuscular blockade was monitored with a force transducer which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz, delivered for a duration of 0.15 ms via 25-gauge needles placed subcutaneously. A strip chart continuously recorded the force transducer measurements from 10 min before to 50 min after succinylcholine administration. The times to initial twitch depression and to maximal neuromuscular blockade and the magnitude of neuromuscular block were measured, as were times to 10, 25, 50, 75, and 90% recovery of initial twitch height. Student's ttest was used to test statistical significance

between groups, with p<0.05 considered significant.

Results. Maximal neuromuscular block (twitch height depression) and the times to initial and maximal twitch depression for the 2 groups are shown in Table 1. There was no significant difference between the two groups for these measurements. The times to various % recovery, a measure of duration of neuromuscular blockade, are shown in Table 2. There was no significant difference at any % recovery of initial twitch height between patients given cimetidine and controls.

<u>Discussion</u>. Cimetidine is known to alter the effects of many drugs commonly used in anesthesia including narcotics (4), benzodiazepines (5), and beta blockers (1). Proposed mechanisms for cimetidine-induced changes are a reduction in liver blood flow (1) and inhibition of liver microsomal enzyme systems (2). After IV injection of a dose of

succinylcholine, the drug is distributed throughout the extracellular space and to the neuromuscular junction. The plasma level and the clinical effects of succinylcholine dissipate because of enzymatic breakdown in the plasma. Because of the demonstrated inhibition of pseudocholinesterase in vitro by H₂ antagonists (3), it is reasonable to anticipate an interaction between cimetidine and succinylcholine. Indeed, one recent study (6) showed a markedly prolonged time to recovery of neuromuscular function in patients receiving cimetidine versus controls during halothane anesthesia. However, we found no differences in onset or duration of succinylcholine-induced neuromuscular blockade between cimetidine-treated and control groups. The reason for the discrepancy between our results and those reported previously (6) is unclear. Further exploration of a possible cimetidine-succinylcholine interaction appears warranted.

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Table 1

	Maximal	Time to Initial	Time to
	Block	Twitch Height	Maximal
	(%)	Depression(min)	Block(min)
Cimetidine	98.0±6.3	0.7±0.3	1.4±0.7
Control	98.8±3.8	0.7±0.2	1.6±0.4

All values are mean ± SD

Table 2

	10%	Time (m ⁻ 25%	in) to F 50%	Recovery 75%	90%
Cimetidine	7±2	8±2	9±3	10±3	10±3
Control	7±2	8±2	9±3	10±3	11±3

All values are mean ± SD

Title: THE CO2 RATE OF RISE DURING FENEA IN ANESTHETIZED HUMANS WITH AIRWAY OBSTRUCTION

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Introduction. Studies in anesthetized men during apneic oxygenation (ApOx) have revealed PaCO₂ rates of rise ranging from 3.2 mmHg/min to 5 mmHg/min. 1.2 During ApOx, the continual O₂ supply to the airway may eliminate CO₂, even if the flow is very low. 3 Awake, apneic humans with a closed glottis have a 6 mmHg/min CO2 rate of rise after an initial rise of 9 mmHg during the first 20 sec of apnea. This apparently higher rate was attributed to wakefulness and to a closed glottis, so that no CO2 could be eliminated by a continuous gas flow. The purpose of this study was to determine anesthetized humans' PaCO2 rate of rise when the lungs receive no gas flow to promote CO2 elimination.

Methods. Fourteen healthy adults consented to participate in this institutionally approved investigation. Arterial oxyhemoglobin saturation (SaO₂), arterial blood pressure, and ECG were displayed continuously. Thiopental 4 mg/kg iv induced anesthesia; succinylcholine 1 mg/kg facilitated tracheal intubation. Then, patients were ventilated with O2 and enflurane for at least 10 min, until neuromuscular function recovered, and until enflurane anesthesia was deep enough to prevent spontaneous ventilation with normal PaCO2. No N₂O or other muscle relaxants were used.

Next the tracheal tube was occluded with a clamp. Arterial blood samples for pO_2 , pCO_2 , pH, and SaO_2 analyses were obtained at the time that the tube was clamped, and 20, 40, 60, 120, 180, 240, and 300 sec thereafter, or until the pulse oximeter SaO2 decreased to .93, the patient attempted to breathe, or 5 min elapsed. Then the tracheal tube was unclamped, the normal conduct of anesthesia was resumed, and the surgeons began the operation.

Multiple mathematical curves were fit to the data to derive an equation that described the PaCO2 rate of rise. The equation which resulted in the least sums of squares was chosen as the best fit. The initial and terminal slopes of that equation were estimated.

Results. Patients ranged in age from 24 to 80 yrs (36 + 14 yrs; X + SD), and were apneic with an occluded airway for a mean of 224 sec. All patients remained apneic for at least 120 sec, 7 remained apneic for 300 sec. No patient's heart rate or rhythm, or systemic blood pressure varied luring the study. No patient's SaO2 fell The figure depicts the equation pelow .92. which best fit the PaCO2 rate of rise:

 $PaCO_2 = (PaCO_2)o + .044(t) + 2.72[ln(t)]$

where (PaCO₂)o = initial PaCO₂ (mmHg) and t = duration of apnea (sec). PaCO2 rose 12 mmHg during the first min, and 3.4 mmHg/min thereafter.

Discussion. As observed previously, PaCO₂ rose logarithmically. The equation which best related PaCO2 and time was reduced to two linear estimates so that these results would be clinically useful and could be compared to those of previous works. Eger and Severinghaus made the first nonlinear estimate of PaCO2 rate of rise during ApOx: 13mmHg during the first minute, and 3mmHg/min thereafter - nearly identical to our results. Thus, ApOx did not eliminate significant quantities of CO2; and, the higher CO2 rates of rise that we observed in awake humans with closed glottides were mainly due to wakefulness. Therefore, the CO2 rate of rise in awake humans appears to be twice that of anesthetized humans. Because mixedvenous pCO2 exceeds PaCO2 by 5 mmHg, another mechanism must be partially responsible for the initial 12 mmHg rise. The PaCO2 rate of rise derived from this study (12 mmHg for the first min, and 3.4 mmHg/min thereafter) should be used when the duration of apnea is estimated from change in PaCO2, or when duration of apnea is prospectively estimated in anesthetized patients.

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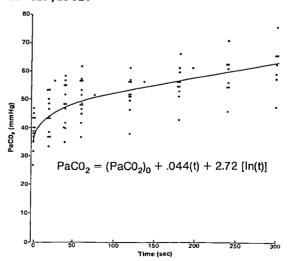


Figure. Duration of apnea (time) and PaCO2 in anesthetized patients.

TITLE: SPONTANEOUS DECLINE OF CEREBRAL BLOOD FLOW DURING HYPOTHERMIC CARDIOPULMCNARY BYPASS AUTHORS: D.A. Stump, Ph.D., A.T. Rogers, M.B.Ch.B., D.S. Prough, M.D., G.P. Gravlee, M.D., S.

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<u>Introduction</u>: Numerous factors affect cerebral blood flow (CBF) during cardiopulmonary bypass (CPB), including PaCO₂ and temperature (1,2). This investigation determined that during CPB, CBF spontaneously declines.

Methods: After the study was approved by the Clinical Research Practices Committee, written informed consent was obtained from 6 patients undergoing cardiac surgery. Those with hypertension and cerebrovascular disease were excluded. Premedication constraints and im morphine. Fentanyl 75 µg.kg induced facilitated narcosis and pancuronium 0.1 mg.kg facilitated endotracheal intubation. Except for 02, no additional drugs were given until completion of CBF measurements. During CPB, PaCO₂ was held at approximately 27 mmHg, corrected for nasopharyngeal temperature (NPT), while mean arterial pressure (MAP), NPT, pump flow (Q), and hematocrit (Hct) were maintained within narrow limits. CBF determination during CPB employed clearance of 133Xe injected through the arterial infusion line. Clearance curves were obtained from 16 cadmium telluride gamma detectors. CBF calculations used the CBF₁₅ technique, corrected for Hct and NPT. The minimal regional variance between probes allowed us to average values from individual detectors to obtain global CBF. CBF measurements (baseline and after a variable interval) began after cross-clamping of the aorta and stabilization of hypothermia (NPT ≈28°C). Paired 2-tailed t-tests, significant at p<0.05, compared CBF differences. All values are expressed as mean ± standard deviation.

Results: In all patients, CBF diminished during CPB (Figure). Mean global CBF's at baseline and after 32 ± 19.1 min were 15.9 ± 3.5 and 12.6 ± 2.2 ml.100g $^{-1}$.min $^{-1}$, respectively. During both measurement intervals, controlled variables did not change (Table).

<u>Discussion</u>: The observed decrease of CBF with time in CPB patients parallels CBF decreases during repeated measurements in awake, resting subjects (3) and in anesthetized patients (4). Persistence of residual ¹⁵³Xe from the first injection cannot explain this finding. Although the mechanism of this decline remains undefined, the phenomenon must be considered when studying CBF during CPB.

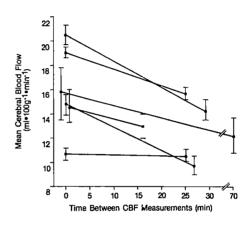


Figure: Data points are mean CBF ± SD of 16 probe locations for each individual subject.

Table: Controlled Variables (mean ± SD)

C	BF	PaCO ₂ * (mmHg)	MAP (mmHg)	NPT (°C)	Q (L/min/m ²)	Hct (%)
#	1	26±3	68±11	26.5±0.8	1.9±.14	22±3
#	2.	28±3	71±10	26.6±0.8	1.8±.14	23±3
	^	corrected	for body	temperature		

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Title:

MYOCARDIAL FUNCTION ASSESSMENT DURING CARDIOPULMONARY BYPASS SURGERY

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Introduction: Although evaluation of cardiac function in man during and after surgery is critical, there is at present no method of continuously monitoring regional myocardial contractility. This study was designed to assess myocardial contractility, using wall thickness changes in humans - a methodology previously validated in animals.

Methods: 10 patients (protocol approved by the Institutional Review Board for Human Research) were included in this study. All measurements were taker prior to cardiopulmonary bypass and were recorded on an 8-channel Gould® polygraph and an 8-channel Gould® tape recorder (Gould, Inc., Cleveland, OH). After thoracotomy an ultrasound Doppler system was used and two types of 10 MHz probes were applied to record cardiac muscle wall thickening: one probe (Alvar Electronic, France) was sutured on the epicardium of the left ventricle and a suction probe (Baylor College of Medicine, Houston, TX.) was connected to a vacuum pump (-30 mmHg). The "Alvar" probe was sutured on the left ventricle close to the apex, between the left anterior descending and the diagonal arteries and was left in place thereafter. The suction probe was first placed on the anterior and inferior walls of the right ventricle and then on the apex, lateral wall, base, and posterior wall of the left ventricle. The thickening of muscle layers was sensed at any desired depth in the myocarlium. The depth of the endocardium in particular was determined by listening to the echo received by the probes. From this position, after the initial measurements, the depth was reduced by half in order to evaluate the epicardium contribution to the thickening. The thickening fraction (TF; expressed in percent) $^{\! 1}$ is derived from the wall thickening by dividing the displacement by the depth of measurement. Data are presented as mean + SEM.

Results: On the left ventricle, a TF of 22.3 ± 3.25 was recorded with the "Alvar" probe (n=10), showing a greater TF of the endocardium (32.5 ± 4.2%) than of the epicardium (15.5 ± 3.4%). The TF recorded with the suction probe on the right ventricle (anterior and inferior walls) and the left ventricle (apex, lateral wall, base, posterior wall) are presented in table 1. These data indicate that on the left ventricle and on the inferior wall of the right ventricle the endocardium contribution to muscle contraction was greater than the epicardium contribution which was not shown at the anterior wall of the right ventricle.

<u>Discussion</u>: These data demonstrate that in humans nyocardial function, and more precisely muscle contractility, can be assessed through the TF. As compared to echocardiography, this method allows continuous measurement of cardiac function during cardiopulmonary surgery. It also allows immediate liagnosis of myocardial dysfunction due to ischemiacy reliminary data indicate that the "Alvar" probe carbe left in place during the postoperative period.

This new method represents a powerful tool for evaluation of the effects of surgery, anesthetics, and drugs on cardiac function during and after cardiopulmonary surgery. Most importantly, our data demonstrate the significance of such an approach for per- and postoperative monitoring of cardiac function in patients undergoing cardiac surgery.

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Am. J. Physiol. 251: H1045-H1055, 1986

Table 1

Right Ventricle

Anterior	Wall $(n=10)$	Inferio	r Wall (n=4)
TM 22.6	+ 3.7	TM 26.	2 + 10
EP 24.6			0 + 7.7
EN 20.5	+ 6.2	EN 33.	2 ± 13.7

Left Ventricle

Apex (n=10)	Lateral Wall (n=10)
TM 19.6 + 2.6	TM 27.1 ± 2.1
EP 16.2 + 2.2	EP 24.2 ± 2.1
EN 24.6 + 4.1	EN 31.6 ± 3.9
Base (n=10)	Posterior Wall (n=10)
TM 22.8 + 3.3	TM 22.8 + 3.2
EP 21.5 + 3.3	EP 19.9 + 2.5
EN 23.3 + 5.2	EN 27.5 + 5.7

TM = transmural

EP = epicardium

EN = endocardium

Title:

EFFECTS OF VERAPAMIL AND DILTIAZEM PRETREATMENT ON POTASSIUM RELEASE IN DOGS

FOLLOWING SUCCINYLCHOLINE

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 $\underline{Introduction}.\quad \text{Animal and human studies have demonstrated} \quad \text{that} \quad \text{verspamil} \quad (\mathtt{V}) \quad \text{and} \quad \text{beta}$ adrenoceptor blockade exacerbates the increase in serum potassium (K^+) after acute K^+ loading or following intravenous administration of succinylcholine (SCh). ', It appears that V alters the normal homeostatic mechanism for regulation of serum K levels, it may decrease the net movement of the extracellular K intracellularly. It is not known whether diltiazem (D) produces a similar alteration in the mechanism for serum K⁺ regulation. K⁺ efflux from muscle increases following SCh in dogs and humans. Normally there is a .3-.5 meq/L increase in serum K levels occurring within the first 10 minutes following SCh administration. This study compares the changes in serum K+ level following SCh in V and D pretreated dogs.

Methods. Thirty day conditioned mongrel dogs, each having a chronic tracheostomy and carotid loop performed two weeks prior to the experimental period, were anesthetized with sodium thiamylal and nitrous oxide in oxygen. Arterial and venous lines were placed and normocapnia and normothermia maintained. All dogs received 5 ml/kg/h of normal was given IV to all dogs 10 minutes after induction. Arterial blood was drawn and immediately analyzed for serum K with an ion specific electrode (ILS-501) at the following time intervals: 0, 1, 3, 5, 10, 15, 30, and 60 minutes following SCh administration. Changes in serum K were determined for control, V, and D pretreated animals. V and D were given as a 150 mcg/kg bolus followed by a 5.6 mcg/kg/min infusion. Both calcium channel blockers were started during induction. In order to obtain a normal distribution and homogeneity of variance, we performed a percent change transformation of the positively skewed data. Significance of the change in plasma K was compared within groups, and between treatments, and control groups, with one-way analysis of variance (ANOVA) and Duncan's critical-difference testing.

Results. There was no significant difference in baseline K^+ (time 0) between groups. In the control group, K^+ increased significantly by 5 minutes after SCh and persisted up to 30 minutes increase in K by 1 minute which persisted throughout the study period. Peak increase in K occurred at 30 minutes for all groups. The time course for K change was altered by both T while the V and D pretreated groups had significant increase in K by 1 minute which persisted course for K change was altered by both V and D. However, V at 15 minutes, had K values significantly different from control. There were no differences between V and D pretreated groups and between D and control, for all time periods.

 $\underline{\text{Discussion}}.$ Contrary to Roth et al. $^{\!3},$ our investigation shows that V and D pretreatment, in the dose used, affect the pattern of release of K following SCh. There is an early and prolonged increase in K levels after SCh. Although there uncrease in K levels after SCh. Although there was no significant difference between the two treatment groups, D pretreatment produced less of an increase in K than V, the latter having the only significantly elevated K from control, perhaps reflecting D's lack of effect on fast sodium channel in low doses that in turn would lead to stabilization of K⁺ flux.

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PERCENT CHANGE IN POTASSIUM CONCENTRATION

TIME (min)	CONTROL Mean <u>+</u> SD	YERAPAMIL Mean <u>±</u> sd	DILTIAZEM Mean <u>+</u> sd
0	0±0	0 <u>±</u> 0	0±0
1	8 <u>+</u> 2	1 1±6 ^b	9 <u>+</u> 4 b
3	10±14	12±5 ^b	9 <u>±</u> 4 ^b
5	11±10 b	13 <u>±</u> 8 ^b	11±3 ^b
10	13 <u>±</u> 4 ^h	19±8 ^h	17±4 ^þ
15	14±6 ^b	24±10 ^{ab}	19±5 ʰ
30	19±7 ^b	29±12 ^h	24±9 ^b
60	5±12	19±12 ^b	13±10 ¹

CAPTION. 3 INDICATES A SIGNIFICANT (P<0.05) DIFFERENCE FROM THE CORRESPONDING CONTOL GROUP HEAN. **b** INDICATES A SIGNIFICANT (P<0.05) CHANGE FROM THE TIME ZERO MEAN. SO IS STANDARD DEVIATION.

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fitle: TIME RELATED RENAL CONSEQUENCES OF CAFDLOPULMONARY BYPASS

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Introduction. The problem of renal dysfunction following open heart surgery is quite prevalent and of unquestioned importance. Moderate transient impairment of renal function has been reported to occur in approximately 30% of patients following cardiac surgery. There is a correlation between cardiopulmonary bypass (CPB) time and the occurrence of renal failure. We used free-water clearance and alanine aminopeptidase (AAP), a brush corder membrane bound enzyme of the proximal renal cubules to indicate the degree of renal tubular membrane alteration produced by varying lengths of conpulsatile (NP) bypass time.

Methods. With informed consent and approval rom The Ohio State Human Subjects Review committee, we evaluated 12 patients undergoing cortocoronary bypass grafting. All patients had an jection fraction greater than 45% with normal enal function (as determined by the usual clinical riteria of blood urea nitrogen (BUN) and reatinine). Patients receiving aminoglycosides or ther nephrotoxic medications were excluded. Each atient received their usual cardiac medication long with morphine 0.1 mg/kg and lorazepam 0.04 g/kg as premedication. Hemodynamic monitors onsisting of an arterial line, Swan-Ganz catheter, KG leads, and 2 intravenous cannulae were inserted rior to induction of anesthesia. Fentanyl (F) 50 cg/kg and a combination of 0.05 mg/kg pancuronium nd 0.05 mg/kg vecuronium was used for induction of nesthesia. Maintenance consisted of a 0.5 cg/kg/min F infusion and 100% 0. Following nduction, a urimeter was connected for continuous rine output measurement. CPB was instituted using Sarns pump with flows maintained between 2.2-2.4 /M²/min and pressures between 50-80 mmHg on CPB. rine and serum samples for osmolality and etermination of urine AAP levels were obtained efore induction, during CFB, and daily for 2 days ollowing surgery. Free-water clearance was alculated according to the standard clearance ormula. Urine AAP levels were determined using n enzymeimmunoassay method, while urine and serum smolality were determined by freezing point epression. Statistical analyses were performed sing the one-way analysis of variance (ANOVA) with uncan's critical-difference testing. An exact robability test value of p < 0.05 was considered tatistically significant.

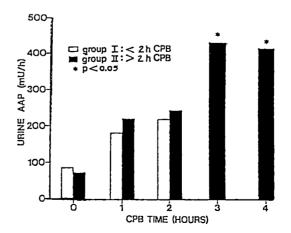
Results. Patients were divided into long (>h) and short duration (< 2h) CPB, there were 5 and patients respectively in each group. There was a significant difference in baseline urine AAP ancentration between groups. Once on CPB, mean reterial blood pressure was maintained between 50-1 mmHg, AAP concentrations were significantly levated from baseline and remained elevated roughout the study in both groups. There was no ifference in AAP concentrations between and within roups for bypass times < 2h, however, long ration CPB patients had significantly elevated

enzyme concentration (p < 0.05) for bypass times > 2 h compared to concentrations < 2h (see figure). There was no significant difference for day 1 and 2 AAP concentrations between groups. Three patients experienced serum creatinine elevations greater than 0.5 mg/dl. There was no significant difference in free-water clearance or urine and serum osmolalities between groups.

Discussion. The length of CPB has been one of the many variables known to affect the incidence of renal dysfunction following coronary artery bypass graft surgery. The length of time necessary to produce this effect is not known, however most agree that CPB times around 4 hours are related to a high probability of renal dysfunction. Our data shows that once CPB exceeds 2 hours, evidence of tubular membrane alteration (is shown by increased urinary AAP) becomes significant. Twenty-five percent of our patients experienced mild transient renal dysfunction which is similar to the incidence of Bhat et al. These patients had CPB times These patients had CPB times greater than 2 hours, their enzyme levels collected after 2 hours of CFB were significantly elevated compared to the levels collected before 2 hours, however their free-water clearance remained negative throughout the study period. None of our patients experienced perfusion pressures below 50 mmHg on bypass. Surgical techniques to reduce mmHg on bypass. bypass time or methods of perfusion that preserves renal homeostasis (pulsatile perfusion) would seem beneficial to the patient undergoing prolonged CPB.

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Title: INTRAPLEURAL BUPIVACAINE VS SALINE AFTER THORACOTOMY - EFFECTS ON PAIN AND LUNG FUNCTION - A

DOUBLE BLIND STUDY

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Introduction. Intrapleural (IP) analgesia with local anesthetics has been consented to be a useful means for post-thoracotomy pain relief (1,2). To evaluate the effects of IP bupivacaine versus placebo (saline) on pain relief and pulmcnary function in the postoperative period after thoracotomy, we studied this in a randomized, double blind fashion.

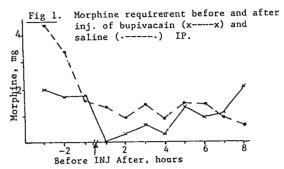
Methods. After approval by the Human Research Committee and written consent, 15 adults (23-74 years) undergoing elective thoracotomy and lung surgery were randomized into control (saline, n=8) or study (bupivacaine, n=7) groups. Anesthesia consisted of Pentothal, pancuronium, 0, and isoflurane. The intrapleural catheter (epidural type) was placed preop with the tip posteriorly. with the patients awake, Postcperatively, horizontal, and the chest tubes under water seal, bupivacaine (1.5 mg/kg b.w.) or saline was injected in the catheter. Fifteen min later change in position was allowed and chest tube suction was restarted. Each catheter was injected twice with 8 hrs interval. Pain was recorded hourly with a visual analogue pain score (VAS), before and up to 8 hrs after each IP inj. (Scale 0-100, 0-no pain, 100-unbearable pain) Additional pain relief was given as i.v. morphine and recorded. Blood was sampled before, 5, 10, 20, 30, 60, 120 and 180 min after IP inj for bupivacaine levels in patients.

Blood gases were followed before and 1,2, 8 and 24 hrs postop and the Alveolo-arterial O₂ gradient (A-aDO₂) calculated. Spirometry with forced vital capacity (FVC), forced expiratory volume one second (FEV), peak flow (PF) and forced expiratory flow 25-75% (FEF) was performed preop and 1,2,4,8 and 24 hrs postop, and before and 30 min after each IP inj.

Statistical analysis was performed with Wilcoxon's test and Paired and Unpaired Student's t-test.

Results. The control group (CON) and bupivacaine group (BUP) were comparable with regard to age, sex and duration of surgery. The pain score (VAS) decreased after each inj in the BUP group (p<0.01). In the controls VAS varied without relation to IP inj. One hour after IP inj the BUP group had significantly lower VAS compared to the controls (p<0.05). Also the mean time from inj til the VAS reached preinj levels was significantly longer in the BUP group (4 hrs) compared to CON group (1-3 hrs) (p<0.05). In the BUP group the morphine requirement dropped significantly after the IP inj, (p<0.05-0.01), Fig 1, but not in the CON group. During the two hrs following each inj the morphine requirements was significantly lower (p<0.05-0.01) in the BUP group. Also the mean time from the IP inj til morphine was requested was longer (4 hrs) in the BUP group compared to the controls (1.5-3.8 hrs) (p<0.01).

Mean bupivacaine levels were 0.8 $\mu g/ml$ plasma after 5 min and rose to 0.88 $\mu g/ml$ at 30 min and decreased to 0.51 $\mu g/ml$ at 180 min. The individual variation in peak time was from 5-30



min. Patients with the highest levels also had the lowest pain scores. The A-aDC₂ increased from the preop period (~25 mm Hg) to the postop period (70-140 mm Hg) in both groups. There was no significant difference between the groups. Spirometric measurements (FVC, FEV, PF, FEF) all dropped significantly one hr postop to 24-30% but rose to 34-45% of preop levels 24 hrs later in both groups. Measurements done before and 30 min after the IP inj showed significant increases in FVC, FEV, PF and FEF in the BUP group but no change in the CON group (Table 1).

<u>Table 1</u>. Mean spirometric measurements in % of preop, before and 30 min after IP inj of bupivacaine (BUP) or saline (CON).

•		Injecti	on 1	Inject	tion 2
		Before	After	Before	After
FVC	BVP	33	47	31	39
	CON	33	33	32	33
FEV	BVP	33	47	34	42
	CON	32	33	30	31
Peak	BVP	35	43	38	41
flow	CON	36	34	31	33
FEF	BVP	36	46	40	43
	CON	35	35	30	30

Discussion. If pain relief with bupivacaine postthoracotomy has the problem with chest tubes that an unknown amount drains out of the pleura. Others have clamped the chest tubes (1) but we feel that is not safe in all patients. We disconnected the tubes from suction but kept them under water seal. This seemed to shorten the duration of the block to about 4 hrs, which is shorter than earlier reports of 4-8 hrs duration. Also our blood levels were lower than earlier reported (1).

Conclusion. At the time the block was working the patients had good pain relief experienced subjectively and also verified objectively with lower pain score, less morphine requirement and significant improvement in pulmonary function tests.

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Fitle: CPK, LDH AND THEIR ISOENZYMES IN THE PER ■PERATIVE PERIOD

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Introduction. The serum level of creatine phosph -:inase (CPK) and its isoenzyme MB, and lactic dehydogenase and its isoenzymes $\mathtt{LDH_1}$ and $\mathtt{LDH_2}$ are used a: markers in the diagnosis of acute myocardial infarcton (AMI). Total serum CPK is also elevated in maligant hyperthermia (MH). Surgical procedures may incease the serum level of these enzymes as well. .1though changes in CPK and MB following open heart urgery have been studied (1,2), a complete picture f the changes in CPK, LDH and their comparison with hose in AMI and MH are lacking. This information is seful to anesthesiologists and other clinicians ecause it may serve to distinguish enzyme changes ir H and AMI of the perioperative period from those due o surgical interventions. Therefore, the present tudy was undertaken to determine the pattern of CPK. DH, and their isoenzymes in the perioperative perioc.

Methods. Thirty patients aged 26 to 75 years, ndergoing orthopedic operations, were included in his study. Institutional approval and informed conent were obtained. The surgical procedures consistec f hip arthroplaties, knee arthroscopies and arthroomies, lumbar or cervical diskectomies, fracture epairs by open reduction and internal fixation, and orrection of acquired joint deformities. The operatons lasted from 30 minutes to 5 hours with a mean of .6 hours. Blood samples were drawn before and immedately after induction of anesthesia, and serial samles after skin incision such that ten samples were rawn over a time span of seventy hours (Tables). ach sample was analyzed for total CPK and its isonzymes (MM,MB and BB) and total LDH and its isoenzyes (LDH₁, LDH₂, LDH₃, LDH₄, and LDH₅). Data were nalyzed using repeated measurements analysis of ariance and Newman-Keuls test. P values less than .05 were considered statistically significant.

Results. Serum CPK and its isoenzymes are preented in Table 1, and LDH and its isoenzymes in Table . The preinduction mean CPK level of 141 units/L $\,$ icreased gradually and significantly after skin icision and reached the maximum level of 809 units/L 1 hours after incision, $p \le 0.005$, and was still sigificantly high at 70 hours (618 units/L, p<0.005).In II, the CPK peaks at about 24 hours after the onset : infarction (3). The pre- and post-induction values ere not significantly different (p>0.05). The highit individual CPK level was in a 27-year-old man who d anterior cervical fusion for cervical myelopathy, d CPK rose to 2570 units/L at 58 hours after incison. The MM fraction increased slightly while the MB d BB fractions decreased after incision. The preduction mean LDH value of 173 units/L gradually creased after incision and achieved two peak levels .e at 34 hours (203 units/L. p<0.01), and the other 58 hours (210 units/L, p<0.01). LDH $_{5}$ also incread and the maximum values appeared at 10 and 34 h ter incision (p<0.005). The LDH_1/LDH_2 ratio did not verse. None of the patients developed signs and mptoms of AMI or MH intra- or post-operatively. ere was a significant correlation between the level CPK and LDH and the amount of muscle damage (r=0.8 d p<0.05). The amount of muscle damage was assesed the basis of type of opeartion and duration of the eration.

Discussion. The normal pattern of changes in the serum CPK, LDH and their isoenzymes in the perioperative period during orthopedic procedures is presented in this communication. The increase in these enzymes following operation is most probably due to muscle cell damage and release of the intracellular enzymes into the circulation. The mere increase in the serum CPK and LDH in the postoperative period, therefore, is not diagnostic of either AMI or MH. In AMI, the increase in the serum CPK and LDH is associated with an increase in CPK-MB and/or reversal of LDH₁/LDH₂ ratio (3). In MH, although CPK and LDH serum levels rise, other signs and symptoms should be present to confirm the diagnosis (4). (Supported by a grant from Anesthesiology Department, University of Pittsburgh.)

Table 1 (MEAN ± SEM)

	TOTAL CPK (Unit/L)	MM (%)	MB (%)	BB (%)
Preinduction Postinduction Hours after incision:	141±20 121±20	89±1 89±1	2±0.2 2±0.2	1.5±0.2 1.4±0.2
4 10 16 22 34 46 58 70	260±42 415±61 511±78 605±81 809±109 673±92 723±115 618±102	92±1 95±1 95±1 95±1 96±1 96±1 96±1	2±0.2 1.6±0.2 1.5±0.3 1.1±0.15 1±0.1 1±0.15 1.4±0.2 1.2±0.2	1.35±0.3 0.8±0.2 0.7±0.2 0.5±0.1 0.8±0.2 0.9±0.2 0.8±0.2 0.86±0.2

TABLE 2 (MEAN + SEM)

	TOTAL LDH (Unit/L)	LDH (%)	LDH (%)	LDH (%)	LDH (%)	LDH (%)
Preinduction	173±8	21±0.9	41±1	20±0.7	7±0.4	12±1.2
Postinduction Hours after	159±9	20±0.9	41±1	20±1.2	7±0.35	11±0.9
incision:						
4	193±11	19±1	37±1.5	18±0.6	9±0.6	17±1.9
10	185±11	18±0.8	35±1	19±0.6	10±0.5	19±1.2
16	197±14	19±0.9	37±1	21±0.6	9±0.6	15±1.0
22	193±15	19±0.9	38±1	21±0.7	9±0.5	15±1.4
34	203±10	19±0.9	34±1	19±0.7	9±0.4	18±1.5
46	186±8	21±0.9	38±1.3	20±0.6	8±0.5	14±1.4
58	210±15	20±0.8	37±1.3	19±0.7	8±0.5	16±1.6
70	190±8	21±1	38±1.4	19±0.6	8±0.6	15±1.7

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Title:

EVALUATION OF PULSE OXIMETRY FOR INTRAOPERATIVE BLOOD PRESSURE MEASUREMENT AND VITAL SIGN

MONITORING DURING PATIENT TRANSPORT VIA LIFE FLIGHT

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Introduction. Life Flight is a popular method to transport critically ill patients. Vital sign monitoring is however difficult in the helicopter. The vibrations of the helicopter interfere with palpation, doppler and oscillometric methods of blood pressure measurements. The noise makes it impossible to hear breath sounds or to obtain blood pressure using Korotkoff sounds. This study evaluated how well systolic blood pressure measured by pulse oximetry correlates with conventional methods of blood pressure measurement (1) and the use of a pulse oximeter (2) for vital sign monitoring intraflight.

Methods. To measure blood pressure with a pulse oximeter, the blood pressure cuff was applied in the usual fashion and the pulse oximeter probe was placed on an ipsilateral phalanx. The Ohmeda BIOX 3700 pulse oximeter was used in this study. The pulse oximeter signal disappears when the cuff is inflated above the systolic blood pressure. When the cuff was deflated slowly, the pressure at which the pulse waveform first reappeared was recorded. Twenty healthy volunteers, 42 anesthetized patients and 11 patients transported by Life Flight were studied.

Systolic blood pressure was measured in the 20 volunteers by three methods: the pulse oximeter (0XIM), palpation (PALP) and Korotkoff (KORT) sounds.

In 42 anesthetized patients systolic blood pressure was measured with the pulse oximeter (OXIM) (n=42) and by intraarterial cannula (ARTC) (n=12), dcppler (DOPP) (n=30) or Korotkoff sounds (KORT) (n=26). Ten separate measurements were performed during the course of the operation in each patient. Pearson's linear correlation coefficients (r) were computed for the data from 20 volunteers and from the pooled data from 42 patients, to determine correlation of the different methods of blood pressure measurement. Blood pressure, heart rate and arterial oxygen saturation were recorded every five minutes in eleven critically ill patients during transport by Life Flight.

Results. The correlation coefficients (r) for

the volunteers are shown ir Table I, and for the patients in Table II. In the helicopter there was no interference from the fine vibrations to the pulse oximeter. We obtained reliable vital signs on 10 cf the 11 patients transported by Life Flight. One patient suffered massive trauma and there were no palpable peripheral pulses and blood pressure was unobtainable by any method.

Conclusion. We found the return of the pulse oximeter wave form to be an accurate way to measure systolic blood pressure intraoperatively. We also found the pulse oximeter a valuable and improved method of vital sign monitoring intraflight.

On several occasions, the pulse oximeter was the only monitor able to obtain vital signs. There was no interference from the noise or vibrations. Monitoring arterial oxygen saturation is also valuable since many of the patients are transported intubated and at night, when an accidental extubation could go unnoticed until bradycardia occurs.

-	TABLE 1	
OXIM-KORT OXIM-PALP KORT-PALP	n 20 20 20	r 0.88 0.87 0.90
-	TABLE 2	
OXIM-DOPP OXIM-KORT OXIM-ARTC DOPP-KORT	n 300 260 120 230	r 0.996 0.958 0.880 0.953

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ſitle:

INCREASE IN EXTRAVASCULAR LUNG WATER AND DECREASE IN LUNG LYMPH FLOW RESULTING FROM POSITIVE

END EXPIRATORY PRESSURE

luthors: Affiliation:

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Introduction. Positive end expiratory pressure PEEP) is used to manage patients with respirators ailure. (1) PEEP improves gas exchange main y increasing functional residual capacity, decreasing pulmonary shunt and recruitment of air spaces he effect of PEEP on extravascular lung water EVLW) remains controversial and has not been we tudied in animals without pulmonary injury. We tudied the effect of PEEP on EVLW and pulmonary ymph flow in an animal model with no pulmonar;

Methods. Twelve sheep with arterial, left. trial, lung water and Swan-Ganz catheters were sed. The lung lymphatic was cannulated and trachestomies were performed. Animals were given ore eek to recover from the anesthetic procedure. he protocol consisted of placing the animals cr ventilator with no PEEP, tidal volume 15 cc/Ec nd a fixed respiratory rate which maintained the rterial PCO_2 5 mmHg below the value obtained cr pontaneous ventilation. Animals were studiec or a two hour baseline period (Period I). Ther EEP was increased to 10 centimeters of water for two hour period (Period II) and then reduce ack to 0 for an additional two hour period (Pericc II). Lymph samples were collected at fifteer inute intervals. Pulmonary arterial (PAP), systemic rterial (MAP) and left atrial pressures (LAP) and heart rate (HR) were monitored continuously. ymph flows were recorded every fifteen minutes. /LW was measured at the end of each study perioc. ne data were analyzed for statistically significans nange using an analysis of variance and Duncan's ultiple range test.

Results. Lymph flow was measured in twelve nimals (Period I). Increase in PEEP (Period II) esulted in a decrease in lymph flow (Figure 1... ne decrease was largest immediately after PEEF is applied. As PEEP was decreased back to 0 (Pericc (I), there was a significant initial increase the lymph flow, which slowly returned back towarc useline values. EVLW was measured in all twelve limals, but reliable data were not obtained at very study period. This was mainly due to technical fficulties in awake, moving animals. Data were icluded only if it was obtained at all three. two consecutive study periods. Data from ter timals were used in the calculation of EVLW values. creases in PEEP resulted in a statistically signicant elevation of EVLW (Figure I). The EVLV lues returned close to baseline when PEEP was :moved.

There was no significant change in cardiectput. When PEEP was increased to 10 cm H₂C. P increased by an average of 5 mmHg, PAP by 9 Hg, LAP by 4 mmHg and PCO₂ by 3 mmHg (Figure . All values returned toward baseline when PEEF s decreased. The increases from Period I to riod II were statistically significant.

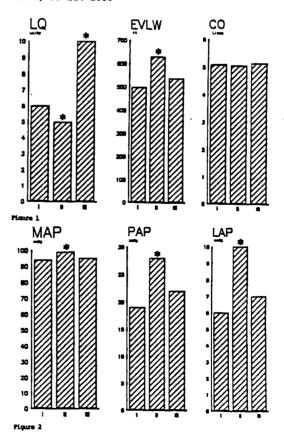
Discussion. In normal animals PEEP resulted in a reversible increase in EVLW and a decrease in lymph flow. We propose that the mechanism for the increased EVLW is due to obstruction of pulmonary lymph flow by increased intraalveolar pressure, causing accumulation of fluid in the interstitial spaces.

Another reported cause for a reversible increase in EVLW is secondary to an effect of PEEP allowing for distribution of thermal indicator through a larger fraction of the lung water. (2) This may have played an additional role in these studies since the changes in EVLW were somewhat greater than the changes in accumulated changes in lymph

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TITLE: THE EFFECT OF TRIMETHAPHAN - NITROPRUSSIDE MIXTURE ON INTRACRANIAL PRESSURE IN CATS

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INTRODUCTION: Sodium Nitroprusside, increases the intracranial pressure (ICP), and therefore is not recommended for patients with increased intracranial pressure (1). A mixture of trimethaphan and nitroprusside (TNP) has been shown to reduce the dose of nitroprusside required to control blood pressure (BP), and thereby decrease the side effects of nitroprusside such as cyanide toxicity, rebound hypertension and tachyphylaxis (2). But its effect on ICP is yet to be determined. Therefore, this study was designed to determine the effect of (TNP) on the normal and increased ICP in cats.

METHOD: Ten cats were anesthetized with isoflurane. Their tracheas were intubated and the lungs ventilated mechanically. A femoral vein was cannulated for drug administration and a femoral artery for blood pressure monitoring and blood gases analysis. The cats were then placed in sphinx position using a stereotactic frame. The scalp and the underlying muscles were dissected and a 5mm hole was trephined in the left parietal area. A catheter was threaded into the subarachnoid space and connected to a pressure transducer for continuous monitoring of ICP. The cats were then divided into two groups: one with normal ICP (N-ICP) and the other with artificially increased ICP (AI-ICP). In the AI-ICP group a size 10F Foley catheter was placed in the epidural space through a 5 $\,\mathrm{mm}$ trephined hole on the right parietal area. Both trephined holes were sealed with bone wax. After completion of surgery the scalp incisions were infiltrated with 2-3 ml of bupivecaine 0.5% and the isoflurane was discontinued. Anesthesia was maintained with nitrous oxide in 30% oxygen supplemented by intermittent doses of pancuronium. The Foley catheter's balloon in the AI-ICP group was inflated slowly with water until the ICP reached a level of 25-30 mmHg and then remained steady. The BP, heart rate, ICP, EKG, end-tidal CO2 and temperature were continuously monitored. The PaCO2 was maintained at 30±2mmHg and the PaO2 above 100 mmHg. Rectal temperature was maintained at 37+0.5 degrees Centigrade. After an hour of stabilization, TNP (trimethaphan:nitroprusside, 3mg:1mg ratio) was infused at 2-10 ug/Kg/min by a pump. The rate of

infusion was adjusted to reduce the BP by 30% for 15 minutes. The highest ICP values, as well as mean BP, heart rate, and EKG before and during the TNP infusion were compared. All measurements were taken at the end of expiration. The zero level for the ICP was referenced to a fixed point at the level of the external auditory meatus. The results were analyzed using Student's paired t-test. P values less than 0.05 were considered significant.

RESULTS: The results are summarized in the Table. TNP produced a dose dependent reduction in mean BP. TNP infusion decreased the BP which reached a steady state within 55±15 seconds. On discontinuation of the TNP infusion, the BP rose to control value within 45±20 seconds. Tachyphylaxis to TNP occurred in one cat and rebound hypertension in another.

1	Norma	.1 ICP	Increased ICP	
1	(N-I	CP)	(AI-ICP)	
İ	BP	ICP	BP ICP	
Control	113 <u>+</u> 9	$2.\overline{6+0}.2$	125±5 28.8±1	
TNP	75 <u>+</u> 10*	4.0 <u>+</u> 0.4*	89 <u>+</u> 6* 37.6 <u>+</u> 0.9*	

*P<0.05

Table: The effect of TNP on mean BP mmHg (MAP) and ICP mmHg in cats with normal and increased ICP.

<u>DISCUSSION</u>: The TNP mixture produces less side effects than either of its component administered separately. But our results indicate that TNP like nitroprusside, increases the ICP significantly. Therefore, TNP should be used judiciously in patients with increased ICP.

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Title: THE EFFECTS OF A NEW MUSCLE RELAXANT, DOXACURIUM, ON LEFT AND RIGHT VENTRICULAR PERFORMANCE

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Introduction Doxacurium chloride is a new, long-acting, non-depolarizing muscle relaxant. It has potential advantages over currently available agents because its effects are non-cumulative and it appears to be devoid of cardiovascular effects in healthy volunteers. In a previous study we demonstrated that Doxacurium, when administered at a dose of twice ED95 to ASA III or IV patients scheduled for cardiac surgery, produces small but statistically significant decreases in heart rate (HR), mean systemic (MAP), mean pulmonary arterial (MPAP), central venous (CVP), and pulmonary capillary wedge pressures (PCWP). To inve To investigate the mechanism of these hemodynamic changes, the effects of Doxacurium on left and right ventricular performance were studied in a similar but larger group of patients.

Methods Fifteen patients scheduled for elective cardiac or major vascular surgery were included in the study. The protocol was approved by the Institutional Review Board and each patient gave written informed consent. The patients were premedicated with combinations of morphine (0.08 to 0.10 mg/kg IM), scopolamine (0.003 to 0.005 mg/kg IM), diazepam (0.07 to 0.15 mg/kg PO) or lorazepam (0.5 to 4.0 mg IM) as determined individually for each patient. Cardiac medications were continued up to the time of surgery. Each patient was monitored by electrocardiographic lead V_5 , and radial and pulmonary arterial catheters (PAC). The PAC was equipped with a rapid response thermistor to measure cardiac output (CO) and right ventricular ejection fraction (RVEF). Stroke volumes (SV), right ventricular end-diastolic volumes (RVEDV) and end-systolic volumes (RVESV) were derived from these variables. After induction of anesthesia (fentanyl, 30-75 ug/kg, diazepam, 2.5-20 mg, succinylcholine, 1 mg/kg, and 100% 0_2) and intubation, a 3.5 mHz 2-dimensional esophageal echotransducer was positioned to obtain a short-axis view of the left ventricle at the level of the papillary muscles. Hemodynamic and echo measurements were recorded at this time (baseline-B) and 2, 5, and 10 minutes after a bolus of 50 or 80 ug/kg of Doxacurium. Left ventricular end-systolic area (LVESA) and end-diastolic area (LVEDA) were subsequently measured by a "blinded" observer using a light pen and interactive computer. Left ventricular ejection fraction area (LVEFA) was calculated as: LVEDA-LVESA/LVEDA. Data were analyzed by repeated measures ANOVA and significance was defined as p < 0.05. All values are expressed as mean ± standard deviation.

Results The administration of Doxacurium produced significant changes in HR, MAP, MPAP, PCWP, and CVP (Table). No statistically significant changes were observed in right or left ventricular dimensions or ejection fractions. No complications or allergic reactions were attributable to the drug.

Discussion Although many muscle relaxants produce significant hemodynamic disturbances, their effects on right or left ventricular performance have not been extensively investigated. With the availability of accurate, clinical techniques to assess ventricular performance, the conventional hemodynamic evaluations of new drugs should be complemented by these measurements. The indices of ventricular function obtained in the current study were within the normal range and, despite minor hemodynamic variations, remained unchanged after Doxacurium. In conclusion, at a dose of 50 or 80 ug/kg, Doxacurium has no discernable effects on right or left ventricular performance.

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TABLE

		В	2'	5'	10'
HR	(BPM)	51±8	51±8	50±8	49±8**
MAP	(mmHg)	70±10	66±10**	70±8	70±10
MPAP	(mmHg)	19±4	18±3	17±3*	17±3*
PCWP	(mmHg)	14±3	12±3***	12±3***	12±3***
CVP	(mmHg)	10±4	8±3**	8±3**	8±3**
CO (I	/min)	3.42±0.73	3.23±0.55	3.23±0.70	3.14±0.61
RVEDV	(m1)	178±49	183±50	189±59	199±75
RVESV	(ml)	116±44	117±43	124±51	134±67
RVEF	(%)	36±8	37±7	36±8	35±8
LVEDA	(cm ²)	17±6	17±5	16±5	17±4
LVESA	(cm ²)	8±5	8±4	8±4	9±4
LVEFA	(%)	54±18	54±12	52±14	50±12
* p <	0.05	** p < 0.01		*** p < 0.001	

DECREASE IN SENSITIVITY TO KETAMINE IN WAR-WOUNDED: INCIDENCE AND COUNTERACTING

EFFECT OF PENTAZOCINE

Authors:

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Introduction: In war surgery, in repeated surgical procedures, ketamine is the drug of choice. Several reports have described the development of tolerance to ketamine during multiple administration of the drug in animal and man (1, 2, 3).

Details concerning the incidence of development of tolerance as well as the responsible mechanism are not clearly expounded in the literature. The purpose of this study was to evaluate, in humans, the incidence of the decrease in sensitivity to ketamine and to ascertain the increase of dose required to produce the same effect as the initial dose. In addition the study verified if a partial opiate agonist (pentazocine) could counteract the decreased sensitivity.

Patients and Methods: 861 war-wounded male patients were included in this study (average age 22,3 \pm 0,6 S.D.).

The repeated anaesthetic procedures were for treatment including: debridement, dressings, delayed primary suture. Patients who underwent less than 3 anaesthetic procedures in their first week after admission were excluded from this study. The amount of ketamine injected in the first ten minutes was the minimum possible to achieve a state of no signs of withdrawal and/or vocal reaction to pain stimulus (initial start of 1-2 mg/kg bodyweight i.v.). When a patient, during repeated surgery required more than 10 mg/ kg-1 bodyweight as a dose, it was decided, for the subsequent procedure(s), to pretreat with pentazocine (0,25 mg/kg⁻¹ bodyweight i.v.).

Results: 861 Patients were included. The average number of anaesthetic procedures with ketamine was 4.56 (+ 0,6). 6 Patients developed decreased sensitivity to ketamine (fig. 1). 4 Patients needed additional anaesthetic procedures after they had reached the level of 10 mg/kg⁻¹ ketamine as an required initial dose. In these patients, after pretreatment with pentazocine, in subsequent surgical procedures, a normal dose of 1-2 mg/kg⁻¹ bodyweight of ketamine was sufficient again.

Discussion: This study gives an incidence of decreased sensitivity of 6,96 per 1000 patients. The first signs of decreased sensitivity in all patients began already after two anaesthetic procedures. In the literature it has been suggested that after decrease of sensitivity, in order to achieve the same effect as in the primary procedure, a 25-30%increase should be sufficient (3). In this study however, increases of up to 500% were required. After pretreatment with pentazocine the patients were as sensitive to ketanine as they were before the decrease in sensitivity developed. This phenomenon supports

the hypothesis (1) that a "central nervous tolerance" alters the effect of ketamine, while it is known that the effect of ketamine and pentazocine is associated with the same opiate neuronal processes (4, 5).

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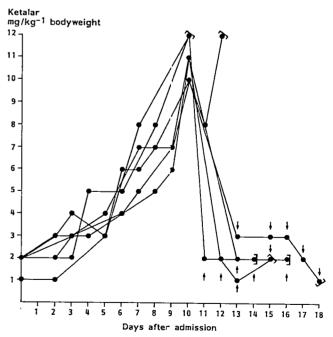


Fig. 1: Required dose of ketamine (ketalar) for repeating surgical procedures in 6 patients who developed a decrease in sensitivity to ketamine. (↓):required dose of ketamine after pretreatment with pentazocine (0.25 mg⁻¹ BW i.v.)

TITLE: ANALGESIC EFFECT OF INTRATHECAL KETAMMINE IN PRIMATES

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Introduction. Epidural administration of ketam re has been shown to produce effective analgesia in patients with postoperative pain (1). The present study was undertaken to evaluate the antinociceptive properties of intrathecal administration (IT) of ketam re in monkeys, an animal model much akin to humans.

Method. The study was conducted after institutional approval and adhered to the regulation of the animal research committee. Seven adult monkeys (Maccaca Cyclopis Swinhoe) weighing 6-8 kg with surgica ly implanted indwelling intrathecal catheters without neurological damage from this surgery were used in this study. With the monkey standing in a specially constructed cage, analgesia was tested using a hot plate test. The monkey normally would stand on a hct plate maintained at 55°C and withdraw its legs when thermal pain exceeds its tolerance. For comparison. the hot plate withdrawal latency (HPWL) time measured were converted to maximal percentage effect (MPE): MPE = (post-injection response latency—predrug response latency)/(cut-off time—predrug response latency) x 100%. The cut-off time in this study was 40 seconds to avoid damage to the feet tissue. The study procedure was divided into three phases. Phase I: 45 a comparative control, morphine sulfate 1 mg was administered intrathecally and its analgesic effect was measured by the hot plate test. Phase II: one week later, 3 different doses of preservative free ketamine (5, 7.5 and 10 mg) were given intrathecally with 7 days lapsing between each dose and the analgesic effect was assessed as above. Phase III: to ascertain the systemic effect of ketamine, ketamine 30 mg IM was given and its analgesic effect was tested in the similar fashion two weeks after the intrathecal drug administration. The HPWL was measured before (time 0), and at 5, 10, 15, 30, 60, 90, 120, 150, 120 and 240 minutes postdrug administration for each drug. The mean arterial blood pressure, pulse rate, respiratory rate, sensorium, and behavior changes were also recorded throughout the observation period.

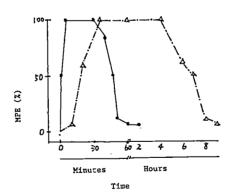
Results. Intrathecal morphine produced potent analgesia with an onset at 30 minutes and duration of action lasting 5.5 hours (Fig 1). Intrathecal ketamine showed a dose dependent analgesic effect with 5 mg producing no noticeable effect and 10 mg producing marked analgesia, peaked at 5 minutes and lasted about 30 minutes (Fig 2). There was sensory block and motor paresis of the legs as tested by forcep pinch and motor reflex associated with ketamine 10 mg IT. Ketamine 30 mg IM also produced analgesic effect with onset at 6.3 minutes and duration about 10 minutes associated with marked drowsiness. All animals recovered from the administration of the test drugs without observable neurological sequale. Autopsies performed on 2 of the monkeys which died from unrelated cause many weeks later showed no microscopic pathology in the spinal cord.

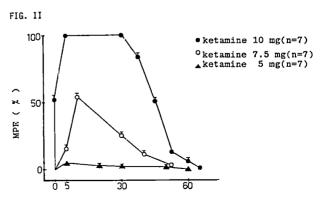
Discussion. Intrathecal ketamine produces potent analgesia and its mechanism of action appears to be threefold: a systemic effect (2), a direct effect on the opiate receptors in the spinal cord (3), and a local anesthetic effect as demonstrated in our animal model. Eventhough intrathecal ketamine has a theoretical advantage of lack of respiratory depressing

effect, its much shorter duration of action when compared to that of morphine and the resultant motor and sensory block make it distinctly undesirable as a substitute for intrathecal morphine for pain relief. Furthermore, only a small number of safety studies have been reported with the intrathecal administration of ketamine in animals (4). The clinical application of intrathecal ketamine awaits further exploration.

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Time (min)

Title: HIGH DOSE VECURONIUM: ONSET AND DURATION

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Introduction:

Vecuronium, a new steroidal neuromuscular blocking agent, has no histamine release or cardiovascular side effects at several multiples of the ED95. We were interested in defining the onset time, duration, and cardiovascular effects of vecuronium at high multiples of the ED95.

Methods:

Forty adults (ASA status I-II) between 18 and 59 years of age, having low-risk elective surgical procedures were studied. The study was approved by the Protection of Human Subjects Committee; informed consent was obtained from each patient. No patient received aminoglycoside antibiotics or antihistamines within 48 hours of the study. Anesthesia was induced intravenously with thiopental (2-10 mg/kg), midazolam (0-0.2 mg/kg) and fentanyl (1-8 ug/kg). Nitrous oxide (70%), fentanyl, and additional intravenous sedatives were given as necessary to maintain anesthesia.

The ulnar nerve was stimulated supramaximally with repeated trains-of-four stimuli (2 Hz for 2 sec at 20 sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan-Bernett/Datex monitor. The degree of neuromuscular block was characterized as the height of the first response compared to the control response. Time from injection of vecuronium to complete neuromuscular blockade was recorded (onset time).

Patients were randomly assigned to one of four groups to receive 0.1, 0.2, 0.3, or 0.4 mg/kg of vecuronium (Group 1, 2, 3, 4 respectively). Vecuronium was administered through a T-connector into a rapidly running intravenous infusion. Mean arterial pressure (MAP) and heart rate (HR) were measured noninvasively (Dinamap) prior to the bolus of vecuronium and at one minute intervals after the bolus but prior to intubation. Intubation was performed when the blockade reached 100%. Ease of intubation was scored using standard criteria. Blood was drawn for radioenzymatic assay of histamine prior to and at 1, 3 and 5 minutes after administration of vecuronium.

Edrophonium (1 mg/kg with atropine) was given at the completion of surgery if clinically required. EMG monitoring was continued for a minimum of ten minutes after administration of edrophonium. Time of spontaneous recovery to 25% of control (T25) was estimated from the recording. Recovery of EMG was referenced to the final baseline.

Standard errors (SEM) are shown for all mean values. Differences between the groups were assessed by analysis of variance and the Student-Newman-Keuls multiple range test. Differences were considered statistically significant at P \leq 0.05. Results:

There was no difference between dosage groups with respect to age. Onset time was significantly shorter in Group 3 than Group 2; there was no significant difference in onset time between Groups 3 and 4 (table 1). In groups 1 and 2, 1 patient (5%) reached 100% block by 90 sec; in groups 3 and 4, 12 patients (60%) reached 100% block by 90 sec.

The heart rate decreased by a mean of 3.0 ± 1.3 beats/minute. The MAP decreased by a mean of 6.7 (± 1.3) torr; the largest decrease in MAP (12 torr) occurred in Group 3. No patient developed flushing or changes in pulmonary dynamic compliance.

Thirty-nine patients had excellent intubation scores; one patient exhibited some mild diaphragmatic movement following intubation. There was a general increase in the duration of neuromuscular blockade with increasing dose; however, only the differences between groups 1 and 3 and groups 1 and 4 are statistically significant. If the train-of-four ratio (T4/T1) was at least 0.02 when the patient was given edrophonium, the T4/T1 ratio recovered to at least 0.70 within 5 minutes. If the T4/T1 ratio was greater than 0.30 when edrophonium was given, the T4/T1 ratio increased to at least 0.90 within 2 minutes. If the T4/T1 ratio was zero when edrophonium was given 5 of 9 patients failed to recover to 0.70 within 20 minutes. Discussion:

The onset and duration of neuromuscular blockade from vecuronium can be manipulated by variable dosing regimens. Intubating conditions are excellent at all doses once maximum neuromuscular block is achieved. In general, the larger the dose the shorter the onset time and the longer the duration of effect. There is no clinical advantage of using 0.4 mg/kg over that seen from 0.3 mg/kg. A large initial bolus dose (0.3 mg/kg) of vecuronium provides rapid onset of neuromuscular blockade without untoward cardiovascular side effects. At this dose profound neuromuscular blockade may last for several hours in some patients. If T4/T1 ratio is at least 0.02, neuromuscular blockade is easily antagonized with edrophonium.

Table 1: Vecuronium Onset and Duration

Dose (mg/kg)	Onset (sec)	T25 (mins)
0.1	164 <u>+</u> 27 (60 - 360)	42 <u>+</u> 4 (25 - 69)
0.2	120 <u>+</u> 5 (100 - 140)	74 <u>+</u> 8 (51 - 106)
0.3	88 <u>+</u> 5Δ (60 – 120)	111 <u>+</u> 19* (62 <u>-</u> 208)
0.4	78 <u>+</u> 6 <u>0</u> (60 <u>-</u> 100)	115 <u>+</u> 22* (35 - 191)

Mean + SEM (range)

* Significantly different from 0.1 mg/kg \(\Delta \) Statistically different from 0.2 mg/kg Reference:

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Title: EFFECT OF HIGH DOSE FENTANYL ON FLUID ALD VASOPRESSOR REQUIREMENTS AFTER CARDIAC SURGERY

Authors: KJ Tuman, M.D., DM Keane, M.D., AI Silirs, M.D., BD Spiess, M.D., RJ McCarthy, Pharm.D.,

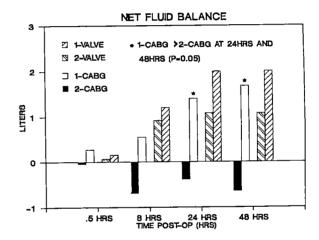
and AD Ivankovich, M.D.

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Introduction. Studies of the effects of high dose fentanyl (HDF) anesthesia for cardiac surgery have focused on the period prior to cardio-pulmonary bypass (CPB); less is known about the post bypass period. High dose morphine has been shown to produce relative hypotension and necessitate large fluid requirements after cardiac surgery. Fluid requirements have been shown to be increased in the immediate postop period after HDF(1) compared to halothane, but other postop variables have not been examined. We studied the effects of HDF on postop cardiopulmonary variables, fluid and vasopressor requirements in patients undergoing cardiac surgery.

Methods. After approval by the Institutional Human Investigation Committee, 30 patients gave informed consent to be randomly assigned to one of 2 groups. Anesthesia for group 1 (1c:N=10 CABG, lv:N=5 valve replacements) consisted of fentany1 75 mcg/kg bolus followed by 0.3 mcg/kg/min infusion. Anesthesia for group 2 (2c:N=10 CABG, 2v:N=5 valve) consisted of diazepam 0.8 mg/kg and ketamine 2 mg/kg for induction followed by infusion of 1 mg/kg/hr ketamine with diazepam 0.07 mg/kg/hr. All pts received vecuronium for intubation and maintenance of neuromuscular blockade; diazepam 0.2 mg/kg po was given 1 hr prior to insertion of femoral arterial and oximetric pulmonary artery catheters. Data collected included hemodynamic profiles, arterial blood gases, SvO2, Hgb, Ca", fluid balance and body wt. These were recorded at standard times from preinduction to 48 hrs postop. In addition, time to awakening (eye opening/hand grasp to command), need for vasoactive infusions and periop MI were noted. Periop fluid administration was guided by PCWP. Post bypass, blood was transfused when Hgb level fell below 9 g%. Hemodynamic data were analyzed using ANOVA with repeated measures in one variable; demographic data using t-tests and χ^2 analysis where appropriate. P < 0.05 was considered significant.

Results. There were no signif. diff. between groups in age, ejection fraction, NYHA class, preop MI, medical problems, medications, aortic cross clamp and bypass times. None of the patients had renal, hepatic or pulmonary disease. There were no signif preCPB differences in HR, MAP, RAP, PCWP, CI, SVR, PVR, LVSWI, RVSWI, PaO, or intrapulmonary shunt Q /Q. Post CPB, Group lc had lower SVR and MAP in the first 12 hrs postop than group 2c (avg diff 19±9 torr, p<0.05) despite a higher net fluid (crystalloid + colloid + blood + blood product minus chest tube and urine outputs, see Figure) and vasopressor requirement (6/10 ingroup 1c and 2/10 in 2c). There was no difference in the use of vasodilator between groups. More pts receiving HDF required diuretics postop (8/10 in group 1c vs 3/10 in 2c, p <0.05) despite no diff. in preop diuretic use. Postop Q /Q, was higher at all times in group 1c than 2c (p<0.05). The above differences between anesthesia techniques were similar in patients receiving valve replacements (lv and 2v). Greater increases in body wt occured at 24 hrs $(2.3 \pm 2.0 \text{ vs } 0.35 \pm 1.0 \text{ })$ kg) and 48 hrs (1.6 \pm 2.1 vs -0.02 \pm 1.3 kg) in group 1c vs 2c. There were no signif. diff. post bypass between groups for HR, RAP, PCWP, CI, PVR, SvO₂, Ca², Hgb or temp at any time postop. Time until awakening was longer in HDF pts (5.0 \pm 2.2 vs 1.7 \pm 1.2 hr in CAB3 pts and 7.1 \pm 3.1 vs 1.5 \pm 1.3 hr in valve pts, p < 0.05). The avg length of ICU stay in HDF pts was longer (104 \pm 40 vs 69 \pm 23 hr, p < .05). There was 1 postop MI (grp 1c).



Discussion. Because of its excellent intraop hemodynamic stability, HDF has become a common anesthetic technique for cardiac surgery. The "stress free" state that is obtained intraop is achieved at the expense of a large amount of residual anesthetic at the end of surgery. Residual HDF may be unbalanced by less noxious stimulation in the postop period and is responsible for sleepy, comfortable, unbreathing patients with lower blood pressures. We have found that HDF for cardiac surgery was accompanied by higher postop vasopressor and fluid requirements with increased Q/Q and longer ICU stay compared to another intravenous technique. Previous work has suggested that choice of anesthetic technique per se (including the 2 compared in this study) has little effect on overall outcome after cardiac surgery . Anesthetic techniques other than HDF may provide less complicated, less expensive postop courses with the same outcome for patients undergoing cardiac surgery. Future studies of physiologic responses to various anesthetic techniques should include their post bypass effects. References.

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Title: DOES PULMONARY ARTERY CATHETERIZATION IMPROVE OUTCOME IN HIGH RISK CARDIAC SURGICAL PATIENTS?

Authors: KJ Tuman, M.D., RJ McCarthy, Pharm.D., AD Ivankovich, M.D.

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Introduction. Catheterization of the pulmonary artery (PAC) is common practice in patients undergoing cardiac surgery. Investigators have shown that therapeutic approaches to patient management is changed in response to PAC compared to CVP . Additionally, in patients with normal LV function undergoing (CABG, CVP monitoring without PAC may be adequate . However, no studies to date have determined whether PAC improves outcome or clinical course in higher risk patients undergoing cardiac surgery. We prospectively examined outcome and course in high risk cardiac surgical patients managed with and without PAC.

Methods. The institutional Human Investigation Committee approved this study of 822 consecutive patients undergoing cardiac surgery who gave informed consent. Patients received either CVP or PA catheters depending on random assignment to anesthesiologist. 5 anesthesiologists managed patients with CVP catheters only and 5 placed PA catheters either before or after induction of anesthesia when indicated. High risk patients (N=447) were divided into 2 groups. Group I consisted of patients with any one of the following indications for PAC: poor LV function (EF < 0.40), CHF at the time of surgery or MI > 6 mo old. Group II patients had any 2 or more of the above indications or were complex cardiac procedures (double valve replacement, CABG plus LV aneurysmectomy) with at least I other indication. Patients who would have otherwise been managed only with a CVP but developed a clinical need for PAC at any time after discontinuation of CPB (defined as a clinically detectable inadequate perfusion state unresponsive to volume infusion, pacing or a single inotropic agent) had a PA catheter inserted (Group III). To determine if placing a PAC before or after a major hemodynamic event effects outcome, Group III was compared to another group (IV) which had received PAC before similar serious hemodynamic events occurred. Perioperative risk factors for cardiac surgery that were noted included the above indications plus presence of unstable angina, pulmonary hypertension, preop renal insufficiency, COPD, life threatening arrhythmias, endocarditis, morbid obesity, MI <3 mo old, diabetes, preop neuro deficit, reoperation, age > 70 yrs, aortic clamp time > 80 min and pump time > 150 min. Each risk factor was assigned a score of 1 point and a risk index (0 to 15) was calculated for each patient to determine if patients receiving CVP or PAC had similar risk profiles. In addition, Group II was divided into a group with 5 or more risk factors (IIb) and one with less than 5 risk factors (IIa) to determine if PAC affected outcome in the sickest of all patients (IIb). Postoperative outcome was judged by in-hospital death, length of ICU stay (>4 days) and postop MI. In addition, the incidence of intraop CV problems (BP <80% baseline requiring vasopressors or low CO state) as well as postop hypotension (requiring vasopressors), use of IABP, pulmonary insufficiency or renal insufficieny were noted. Data was analyzed

using a $\chi^{\,2}$ statistic; p< 0.05 was considered significant.

Results. There were no significant differences in distribution of risk profile scores between CVP and PAC patients in group I or IIb. Patients who received PAC in group IIa had slightly higher risk profile scores than those receiving CVP's. The incidences of in-hospital death and post op MI were not significantly different between patients managed with CVP versus PAC. Prolonged ICU stay was more frequent in patients managed with PAC. The incidence of intraop CV complications, postop hypotension requiring vasopressors, use of IABP post CPB, and risk of pulmonary complications were not significantly different between CVP and PAC in any risk group. Although not statistically significant, the incidence of postop renal insufficiency was higher in group II patients who received PAC. No statistical difference was noted in outcome or postop complications of Groups III vs IV (Table 2).

Table 1. Incidence of Outcome Variables IIa IIb Total CVP PA CVP CVP PA Cases # of pts 100 50 84 54 67 92 822 Death(%) 4.0 4.0 0 0 6.0 10.9 3.2 ICU Stay > 4d(%) 12.1 30.0* 13.1 24.1 29.2 40.4 20.3 Post Op MI(%) 6.0 2.4 3.7 4.6 7.9 4.9

Table 2. PAC Before Versus After Hemodynamic Event
After Event (III) | Refore Event (IV)

	After Event (III)	Before Event (IV)
# of pts	97	80
Death (%)	10.3	12.5
ICU Stay		
> 4d(%)	44.9	36.2
Postop MI	(%) 8.5	9.0

Discussion. Early detection and correction of hemodynamic aberrations with PAC are believed to improve outcome in high risk patients. Our data indicates that in high risk patients undergoing cardiac surgery there was no significant difference in outcome or postop complications in patients with similar risk profiles initially managed with CVP or PAC. However, the incidence of prolonged ICU stay was greater with PAC, perhaps due to clinicians "need" to obtain more physiologic data when a PAC was present. Since outcomes of patients receiving PA catheters before or after a significant hemodynamic aberration were not different, this suggests that high risk patients undergoing cardiac surgery may be managed initially with CVP and then PAC inserted later if needed, without affecting outcome. The latter approach may have an important impact on cost savings in these patients.

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- 2. Mangano DT. Monitoring pulmonary arterial pressure in coronary artery disease. Anesthesiology 1980;53:364-70.

Title: PERIOPERATIVE HEMODYNAMICS USING MIDAZOLAM-KETAMINE FOR CARDIAC SURGERY

Authors: KJ Tuman, M.D., RJ McCarthy, Pharm.D., and AD Ivankovich, M.D.

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Introduction. Although high dose fentanyl (HDF) has become a popular anesthetic technique for cardiac surgery, other techniques may offer similar intraoperative hemodynamic stability. Prior work has revealed that diazepam-ketamine anesthesia produces comparable intraoperative hemodynamics during cardiac surgery, with significant differences in the postoperative period. We have noted increased postoperative fluid and vasopressor requirements as well as times to awakening in patients receiving HDF for cardiac anesthesia. This study was undertaken to compare intra— and postoperative hemodynamics of HDF with the new water soluble intravenous benzodiazapene, midazolam combined with ketamine for cardiac surgery.

1988;67:S1-S266

Methods. The study was approved by the Institutional Human Investigation Committee. 15 patients undergoing elective coronary revascularization gave informed consent and were randomly assigned to receive either HDF (N=10) or midazolam-ketamine (MK, N=5). All patients received diazepam 0.15 mg/kg orally for premedication; femoral arterial and oximetric pulmonary artery catheters were placed prior to induction. MK patients were induced with midazolam (0.5 mg/kg in increments) simultaneously administered with a ketamine infusion (2 mg/kg) over approximately 5 minutes. Maintenance of anesthesia was achieved with continuous ketamine infusion at 1 mg/kg/hr and increments of midazolam (.04 mg/kg/hr). HDF patients received fentany1 75 mcg/kg over 5 min for induction followed by 0.3 mcg/kg/min infusion. All patients received vecuronium for intubation and maintenance of neuromuscular blockade. Data collected included hemodynamic profiles, fluid balance, and body weights. These variables were recorded at standard times from preinduction to 36 hrs postoperatively. In addition, time to awakening (eye opening and hand grasp to command), need for vasoactive infusions, incidence of perioperative myocardial infarction and postoperative emergence phenomena were recorded. Hemodynamic data were analyzed using ANOVA with repeated measures in one variable. Demographic data were analyzed using T-tests and chi-square analysis were appropriate. P < 0.05 was considered significant.

Results. Analysis of preoperative demographic data revealed no significant difference between groups in age, gender, ASA or NYHA class, preop MI, medical problems, medications, aortic cross clamp and bypass times. All patients had left ventricular ejection fractions greater than 0.45 and none of the patients had renal, hepatic or pulmonary disease. As shown in the table there were no significant differences in HR, RAP, PCWP, mean PA pressures, or LVSWI either before or at any time in the 36 hr

period after cardiopulmonary bypass. Patients receiving MK had lower CI than HDF before intubation but no significant difference was noted at any other time. Post-bypass, MAP was significantly lower at all times in the HDF group. There was no difference in the use of vasodilators between groups. More patients receiving HDF required diuretics postop (8 of 10 versus 2 of 5) despite no difference in preoperative diuretic use. Postoperatively, HDF had higher net fluid requirements(crystalloid + colloid + blood + blood product - chest tube and urine outputs) than MK (1786 \pm 2660 vs 40 \pm 514 ml at 24 hrs) and $(1957 \pm 3095 \text{ vs} - 29 \pm 528 \text{ ml at } 48 \text{ hrs}).$ Accordingly, MK patients gained less weight than HDF at 24 hrs (.98±.44 vs 2.3±2.0 kg) and 48 hrs (.36±.28 vs 1.6±2.1 kg.) Use of dopamine for low systemic arterial pressure was less in the MK group (1 of 5 vs 6 of 10). Time until awakening was longer in HDF patients (4.8 \pm 2.2 vs 1.7 \pm 0.3 hr, p < 0.05). There was one perioperative MI, (in the HDF group). No abnormal emergence phenomena or recall were noted in either group. Although not quantitated, there did not appear to be any qualitative difference in postoperative pain, despite rapid awakening in MK

Hemodynamic Variables Table 1. C INTUB STERN PREINTUB HDF MK HDF MK HDF MK HDF MK 76±15 HR 76±12 69±4 72±14 73±7 69±16 71±10 70±6 97±16 91±8 91±15 82±12 93±17 98±7 MAP 96±15 95±14 RAP 7±3 7±4 8+4 9±3 7±3 6±2 8+5 10±4 10±4 11±3 10±5 PCWP 14±6 10±5 15±5 9±5 15±4 PAP 19±7 | 20±5 | 21±7 | 18±4 | 19±6 | 21±8 | 17±5 20±7 CI 2.6±.72.3±.42.7±.82.3±.42.4±.92.3±.32.3±.92.4±.2 LVSWI 41±15 37±8 38±15 33±9 38±19 38±8 40±15 40±11 means ± SD, C=control, Preintub=prior to intubation, Intub=3 min after intubation, Stern=3 min after sternotomy

Discussion. Midazolam-ketamine appears to provide excellent hemodynamic stability both intraand postoperatively for cardiac surgery. When compared to HDF it was associated with less need for postoperative vasopressors and fluids. The rapid emergence from anesthesia is beneficial for physicians and family members who desire to determine neurologic status as soon as possible after exposure to the CNS risks of cardiopulmonary bypass. It appears that this early awakening is unaccompanied by any untoward pain or hemodynamic events, perhaps because of the potent, lasting analgesic properties of ketamine. In summary, our data indicates that midazolam-ketamine offers several advantages over high-dose fentanyl in the postoperative period after cardiac surgery.

References.

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for open-heart surgery. Anaesthetist 1976; 25:457-63.

EFFECTS OF INTRAOPERATIVE ARTERIOVENOUS HEMOFILTRATION DURING ORTHOTOPIC LIVER TRANSPLANTAION Title:

KJ Tuman, M.D., BD Spiess, M.D., RJ McCarthy, Pharm.D., WG Logas, D.O., and AD Ivankovich, M.D. Authors:

SVRI

Affiliation: Department of Anesthesiology, Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois

Introduction. Orthotopic liver transplantation (OLT) remains one of the most difficult challenges facing anesthesiologists today. OLT often involves large blood loss and replacement as well as administration of large amounts of blood products to correct coagulation defects. Renal free H,O excretion is often impaired in end stage liver disease (ESLD) and not responsive to routine diuretic therapy, predisposing to increases in extravascular lung H20 during OLT. Recently, a new technique, continuous arteriovenous hemofiltration (CAVH) has been employed for treatment of fluid excess in critically ill pts where hemodialysis or peritoneal dialysis are not possible. We hypothesized that removal of free H₀0 by intraoperative use of CAVH would improve oxygen transport in patients undergoing OLT.

Methods. This study was approved by our institutions Human Investigation Committee. Ten consenting adults undergoing OLT were anesthetized by rapid sequence induction using etomidate, fentanyl and succinylcholine followed by isoflurane (0.25-2.0%) in 0_2 /air supplemented with fentanyl and vecuronium. Monitors included radial arterial and oximetric thermodilution pulmonary artery catheters. PEEP was applied and adjusted as needed to maintain SaO, > .90 at a nontoxic FIO. CAVH was instituted in 5 pts with poor renal function via the femoral artery and internal jugular vein using a polysulfone membrane hemofilter (Amicon D30S) from which ultrafiltrate was collected. Hemodynamic profiles as well as shunt fraction (Qs/Qt), $C(a-v)0_2$, and $P(A-a)0_2$ were obtained 20 min after incision but before starting CAVH (baseline), 5 min before caval clamping (preanhepatic), 30 min after caval clamping (anhepatic), 30 min after resuming caval flow (recirculation), at end of case and at 24 hr postop. All pts had femoral/portal vein to axillary vein bypass begun prior to caval clamping. Intraop transfusion consisted of PRBC and "cell saver" blood, FFP, cryoprecipitate and platelets, guided by Hgb levels and coagulation tests respectively. Crystalloid was administered to supply Ca[#], HCO₃ and glucose. Cumulative infusate and urine/ ultrafiltrate volumes were noted at end of case. Body wt was noted preop and at 24 hr postop. Inter- val data was compared using ANOVA; other data with Student's t-test; p > .05 was considered significant.

Results. There were no signif. differences in baseline hemodynamics, Qs/Qt, preop diuretic use or duration of anesthesia or surgery between groups. Intraop there were no signif. differences in HR, MAP, CI, SVRI, or PVRI although pts receiving CAVH had signif. lower RAP and PCWP and greater C(a-v)0, in the period after recirculation thru 24 hr postop (see Table). Pts receiving CAVH had signif. decreased P(A-a)O, and Qs/Qt as well as lower PEEP requirements compared to controls (see Figures). Pulmonary compliance was signif. higher after operation in ots receiving CAVH than controls (53.6±3.6 vs 26.7±15.3 m1/cm H_2O , p < .05). There was a net decrease from preop body wt of -4.1 ± 2.7 kg with CAVH vs a gain of 5.8±1.5 kg in controls (p < .001), in accordance with the intraoperative removal of 694±141 ml/hr of

ultrafiltrate. Intraop volume of infusate was not signif. different between groups (576±140 dl vs 550±97 d1 in controls). No complications were associated with the use of CAVH.

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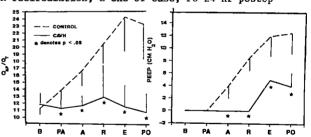
		Control		
Time	В.	R	E	PO
HR (bpm)	87±6	95±9	100±10	97±8
MAP (torr)	81±10	84±8	88±4	84±3
PCWP (torr)	14±4	24±6	23±4	20±3
RAP (torr)	13±4	19±3	22±4	18±2
CI (1/min)	4.9±1.0	4.2±0.6	4.2±0.5	4.4±0.4
SVRI	1120±120	1234±461	1270±195	1203±119
$C(a-v)0_{2}(m1/d1)$	2.95±.32	3.47±.44	3.54±.34	3.42±.31
C(a-v)0 ₂ (m1/d1) P(A-a)0 ₂ (torr)	129±4		361±91	327±89
		CAVH		
Time	В	R	E	PO
HR (bpm)	88±8	93±14	95±15	95±12
MAP (torr)	92±5	92±16	93±17	99±10
PCWP (torr)	17±6	18±5*	16±3*	16±3
RAP (torr)	14±4	14±4*	14±3*	13±2*
CI (1/min)	5.2±0.3	4.6±0.5	4.4±0.5	4.0±0.2

C(a-v)0₂(m1/d1)2.88±.18 3.68±.45*4.54±.47* P(A-a)0₂(torr) 137±21 -- 127±24* 122±16* means ±SD, *denotes p < 0.05 compared to controls B=baseline, PA=preanhepatic, A=anhepatic, R=recirculation, E=end of case, PO=24 hr postop

1193±138 1370±304 1461±356*

1707±128*

4.55±.35*



Discussion. Acute pulmonary dysfunction after OLT is not uncommon when blood loss necessitates transfusion of hundreds of units of blood and products. Pulmonary embolization of microaggregates, low serum oncotic pressure, elevated venous pressures and impaired renal function in pts with ESLD all contribute to hydrostatic and nonhydrostatic pulmonary edema with resultant R to L intrapulmonary shunting. Intraop use of CAVH reduced Qs/Qt, improved oxygenation and decreased PEEP requirements without any adverse hemodynamic effects during anesthesia for OLT. The improvements in pulmonary gas exchange and compliance are most likely due to decreased pulmonary interstitial H₀0. CAVH is a simple technique that can be used by the anesthesiologist in the critically ill patient with impaired renal function even during the intraoperative period. These preliminary results with the intraop use of CAVH are encouraging and suggest the need for further clinical investigation.

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Introduction. Barbiturates, which are known to illosterically enhance the binding of benzodiazepines to he benzodiazepine receptor (1), along with their own mesthetic action also should enhance the anesthetic effect of benzodiazepines. As a result, the conjoint effect of a barbiturate and a benzodiazepine should be nore than the sum of the effects of the two agents acting eparately. The aim of the present study was to find out whether midazolam-thiopental anesthetic interaction is ynergistic.

Methods. Ninety unpremedicated ASA physical status or II adult (21-51 year-old) female patients scheduled for liagnostic curettage or other minor gynecological procedures participated in the study, which was approved by the Institutional Review Board. Three groups were used in the study: one group received thiopental, and two others received either midazolam or midazolam-hiopental combination. Each group consisted of 30 atients. As an end-point of anesthesia the abolition of he ability to open eyes on command was used. If the atient did not respond to the command, she was assumed to be unconscious. The study was carried out doubleilind, the response to the command was checked by an nvestigator who was unaware of what drug or dose was ised. The following predetermined doses of drugs each in ι subgroup of five patients were administered: in the hiopental group $(\text{mg-kg}^{-1}, \text{i.v.}) - 1.7, 2.0, 2.3, 2.6, 3.0, 3.6$; in the midazolam group $(\text{mg-kg}^{-1}, \text{i.v.}) - 0.07, 0.10,$ 1.13, 0.19, 0.26, 0.37; in the midazolam-thiopental group $mg \cdot kg^{-1}$, i.v.) - 0.03 and 0.7, 0.04 and 0.7, 0.06 and 0.7, 1.08 and 0.7, 0.11 and 0.7, 0.15 and 0.7, (midazolam and hiopental, respectively). Patients were assigned to the subgroups randomly. After determination of the endpoint of anesthesia, all patients received another dose of in intravenous anesthetic in order to obtain an adequate lepth of anesthesia before starting the surgical rocedure. The percentages of patients found to be isleep were converted into probit values and plotted igainst logarithmic value for the respective dose. Doseesponse curves were determined with the use of probit malysis (2). To define the type of interaction between nidazolam and thiopental, isobolographic analysis was ised (ED50 level) (3).

Results. The study groups were comparable with respect to demographic charactertistics of the patients. The ED $_{50}$ for midazolam was 0.19 (0.12-0.34) mg·kg⁻¹, and for thiopental - 2.9 (2.5-3.8) mg·kg⁻¹. Comparison of the combined and single-drug ED $_{50}$ doses is presented in the table. In combination, the sum of the fractional doses was significantly lower than a single drug fractional dose 0.5 vs. 1.0, p < 0.001). The ratio of a single drug fractional dose to a combined dose was 2.0. Thus, the lable shows that approximately one fourth of the single frug ED $_{50}$ dose for each of the two agents was needed in combination to induce anesthesia in 50 percent of the patients. The isobolographic analysis used in the present study demonstrated synergistic midazolam-thiopental nter_action for induction of anesthesia (abolition of the response to verbal command).

<u>Discussion.</u> As far as the mechanism for the observed synergism is concerned, several possibilities can be

considered. The benzodiazepine receptor, the GABA receptor, and the barbiturate binding sites are part of a supramolecular complex, and binding of a drug to one of the sites of this complex can allosterically modify the benzodiazepine receptor. It has also been shown that barbiturates enhance binding of benzodiazepines to the benzodiazepine receptor (1). The synergistic anesthetic interaction between midazolam and thiopental may be explained on this basis. Although pharmacodynamic mechanisms seem to be the most likely cause for the synergistic midazolam-thiopental interaction, pharmacokinetic factors cannot be excluded from the consideration. In conclusion, midazolam-thiopental interaction in patients results in a synergism regarding induction of anesthesia.

Table. Midazolam-Thiopental Anesthetic Interaction

Fractional Equi-Effective Doses (ED₅₀) of Midazolam-Thiopental Combination

Groups	Midazolam Component	Thiopental Component	Sum of Fractional Doses	Ratiob
M	1.00 (0.19) ^a	0.00	1.00	_
M+T	0.26 (0.05) ^a	0.24 (0.7) ^a	0.5 p<0.001	2.0
Т	0.00	1.00 (2.9) ^a	1.00	_

M - midazolam group, M+T - combined midazolamthiopental group, T - thiopental group

a - in mg kg⁻¹

 ratio of single-drug fractional dose to combined fractional dose

The p value denotes the significance of the difference between combined fractional dose and single-drug fractional dose.

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Title: Sodium Thiopental To Treat Fentanyl Induced Muscle Rigidity

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Introduction. The purpose of this study was to evaluate the effectiveness of sodium thiopental in abolishing muscle rigidity induced by fentanyl. We also wish to describe a safe and useful human model to evaluate the efficacy of various drugs in attenuating the rigidity associated with high-dose narcotic anesthesia.

Methods. Six adult patients scheduled to undergo major elective surgery were evaluated. The study was approved by the research committee for human studies, and informed consent was obtained. The following monitors were employed: electrocardiogram, blood pressure cuff, peripheral nerve stimulator and transcutaneous pulse oximeter. One hour prior to surgery, the patients were given diazepam, 5 mg orally and morphine sulfate, 5 mg intramuscularly. Upon arrival to the operating suite, up to 2 mg midazolam was administered as needed intravenously, for sedation. A tourniquet was placed on an upper extremity and inflated to 100 mmHg above systolic blood pressure prior to induction of anesthesia. Patients were preoxygenated for 3 minutes, after which time 25-50 micrograms per kilogram of fentanyl was rapidly administered intravenously. Patients were then observed for signs of rigidity, including muscles of the forearm not occluded by the tourniquet, were eliminated from the study. After rigidity was noted to be present, 2 mg/kg succinylcholine was administered intravenously, and its effect on rigidity was documented. At this time the results of peripheral nerve stimulation using a train-offour stimuli were documented. Five minutes after the onset of rigidity, patients were given sodium thicpental (TP) 1.5 mg/kg intravenously. Its effects were noted, as was the response to the train-of-four nerve stimuli.

Results. In all cases where rigidity was noted in one forearm, it was also seen in the contralateral forearm. Succinylcholine administration abolished rigidity in all muscles proximal to the tourniquet after succinylcholine was given. At this time, there were no appreciable twitches seen in the arm not occluded by the tourniquet, while four strong and equal twitches were observed in the forearm occluded by the tourniquet. Within 90 seconds after sodium thiopental administration, the forearm below the tourniquet became relaxed in all cases. Again, there were no twitches observed with peripheral nerve stimulation in the unoccluded forearms, while four strong twitches were seen in the forearms distal to the occluding tourniquets.

<u>Discussion</u>. The mechanism of action of muscle rigidity induced by high-dose narcotic anesthesia

has not been fully elucidated. Studies in animals suggest that it is centrally mediated.(1-2) It has been reported that dopaminergic neurons within the basal ganglia may also be involved.(3) In humans, only muscle relaxants have been shown to attenuate the rigidity in the operating room environment,(4) while narcotic antagonists have been demonstrated as effective in the recovery room.(5) Indeed it has been reported that sodium thiopental is not effective in attenuating the rigidity seen in the extremities, when it is administered before alfentanil.(6)

In this study we assume that the drugs administered proximal to the occluding tourniquet did not leak in to the distally occluded forearm. This is demonstrated by the fact that intravenously administered succinylcholine did not affect the muscles distal to the tourniquet. Accepting this, we have shown that the effect of high-dose fentanyl on rigidity is mediated via a central mechanism, and that this effect is abolished, at least in the muscles of the forearm, by sodium thiopental given after the onset of rigidity. Though the effect of sodium thiopental may be via a generalized central depression rather than a specific antagonism of induced rigidity, it may serve as a useful adjuvant in the treatment of narcotic induced rigidity, until a specific treatment is described. Also, we have found the model described useful in evaluating the effectiveness of various drugs in treating narcotic induced muscle rigidity.

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Title.

COMPARISON OF END-TIDAL CO2 AND FOUR CLINICAL SIGNS FOR THE DETECTION OF ESOPHAGEAL INTUBATION IN FOLENTS.

Authors .

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Introduction: End-Tidal carbon dioxide (ETCO2) monitoring is often quoted as a reliable method for the early detection of esophageal intubation (1-3). However, a systematic study comparing its reliability to some commonly used clinical signs has not been published. This single blind study compared ETCO2 and four clinical signs for the early detection of esophageal intubation.

esophageal intubation.

Methods: Twenty female Wistar rats (mean weight 257 gm; range 226-286) each with a chronically implanted carotid artery cannula were studied. Each animal was anaesthetized with 4% alothane in oxygen and N2O (FIO2 = 0.5). Ten ainutes after induction, simultaneous intubation of the trachea and esophagus was achieved with 4% alothane in oxygen and N2O (FIO2 = 0.5). Ten ainutes after induction, simultaneous intubation of the trachea and esophagus was achieved with 4% Jelco cannulae. The tracheal cannula was irst connected to a Harvard rodent ventilator rate 100/min; tidal volume 4.5 mls) and the mimal was ventilated with 1.5% halothane in an xygen/nitrous oxide mixture (FIO2 = 0.5). ETCO2 readings were taken at 40,50 and 60 sec after commencing ventilation using a Beckman Medical ias Analyzer - LB2 (Beckman; Illinois, U.S.A.) hose function had been previously tested in ats. During the period of tracheal ventilation he animal was closely observed for the presence r absence of 4 clinical signs: symmetrical hest inflation, abdominal distention, moisture round the cannula during the inspiratory phase. fter 1 min of tracheal ventilation, arterial lood gases (ABGs) were sampled and the entilator was then connected to the esophageal annula. Again, the animal was observed for the bove mentioned clinical signs. ETCO2 readings ere taken at 40,50 and 60 sec, and ABGs were hen taken after 60 sec of esophageal entilation. Finally, the tracheal cannula was econnected to the ventilator and the animal was econnected to the ventilator and the animal was entilated with 100% Oxygen until awake. This tudy sequence was used in all animals. The Gold tandard for identifying cannula location in this tudy employed 2 criteria:

a) direct visualization during intubation, and (b) awakening of the animal during intilation with 100% Oxygen at the end of the tudy. In the second part of the study, results or all 5 variables (ETCO2 and 4 clinical signs) are randomly presented either alone or in ifferent combinations to an experienced assektetist who was blinded to the study. He is asked to identify whether the variable/s were stained with tracheal or esophageal intilation. Estimates of sensitivity, secificity, positive predictive value and false siteria for diagnostic tests. Sample size clculation using previously published ETCO2 clues with an alpha (two tailed) of 0.001 and ta of 0.1 yielded a value of N = 6.8. By using animals the confidence intervals of this study in excess of 120%.

Results: Mean ETCO2 readings were: esophageal 0.41% (range 0.1 to 0.7%), and tracheal 2.83% (range 2.2 to 3.6%). Mean PaCO2 values were: pre-intubation 52.3 mmHg (range 34 to 82 mmHg); after I min of tracheal ventilation 27.6 mmHg (range 22 to 37 mmHg); and after I min of esophageal ventilation 42.6 mmHg (range 33 to 52 mmHg).

of esophageal ventilation 42.6 mmHg (range 33 to of esophageal ventilation 42.6 mmHg (range 33 to 58 mmHg).

Table 1 summarizes the performance of all 5 tests for identifying esophageal intubation. All tests had high sensitivity. Abdominal distension and moisture condensation had the lowest specificity.

A positive predictive value (PPV) of 1.0 for ETCO2 alone indicates that it identified all cases of esophageal intubation. All 4 clinical signs had PPVs of less than 1.0. Esophageal rattle was the best clinical signs were utilized together their performance still did not equal that of ETCO2 alone. Adding ETCO2 to the clinical signs raised their PPV from 0.95 to 1.0.

Esophageal rattle was the clinical sign with the lowest false positive rate (0.05) whereas that for ETCO2 was zero. Adding ETCO2 to the clinical signs reduced the overall false positive rate to zero.

Discussion: ETCO2 was perfectly predictive of esophageal intubation and had no false positives. All 4 clinical signs had lower predictive values and none were free of false positives. Chest movement and esophageal rattle were the most reliable clinical signs for detecting esophageal intubation in our animal model. model.

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TABLE 1: Comparison of 5 Tests for Identifying Esophageal Intubation

	ETCO2	Moisture		Abdominal Distension	Rattle	All Clinical Together	
Sensitivity	1.0	1.0	1.0	0.95	0.95	1.0	1.0
Specificity	1.0	0.7	0.9	0.7	0.95	0.95	1.0
Positive Predictive Value	1.0	0.76	0.9	0.76	0.95	0.95	1.0
False Positive Rate	0	0.3	0.1	0.3	0.05	0.05	0
Palse Negacive Rate	0	0	0	0.05	0.05	0	0

TITIE: MOUTH OPENING REDUCTION ASSOCIATED WITH SUCCINYLCHOLINE DURING ENFLURANE ANESTHESIA.

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Introduction: In a previous study on humans, a paradoxical reduction of mouth opening and increase in jaw stiffness during halothane anesthesia was associated with administration of succinylcholine, while similar results were not seen with pancuronium or vecuronium(1). Given the divergent neuromuscular effects of halothane and enflurane as well as the paucity of clinical reports on masseter spasm during enflurane anesthesia, this study examined the effects of succinylcholine and vecuronium on mouth opening and jaw stiffness during deep enflurane anesthesia.

<u>Methods</u>: This protocol was approved by the institutional review committee for human experimentation. Subjects, 2 to 13 yrs of age, scheduled to undergo elective surgical procedures requiring general anesthesia and endotracheal intubation were elligible. Patients with TMJ disease, craniofacial disproportions or neuromuscular disease were excluded. Informed consent was obtained. The subjects were not premedicated, and anesthesia was induced by a separate anesthesia team with a nitrous oxide/oxygen mixture and enflurane. Monitors included ECG, blood pressure cuff, precordial stethoscope, temperature, and ETCO2 probe. Neuromuscular blockade was monitored by transcutaneous stimulation of the ulnar nerve with supramaximal, square wave stimuli at 1 Hz. When a clinically deep level of anesthesia was obtained with 3-5% enflurane, the patient's head was placed in the sniffing position. At time T1 the mask was removed and while the patient breathed spontaneously, mouth opening was accomplished by means of a constant force spring which was connected to a traction device positioned over the which was connected to a traction device positioned over the mandibular incisors. The resulting mouth opening (D1), expressed as the maxillary—mandibular incisal distance, was measured in mm. Next, at the discretion of the attending anesthesiologist, succinylcholine (1.5 mg/kg) or vecuronium (0.1 mg/kg), was infused over 15 s. When the visible twitch was lost completely at time T2, the second mouth opening D2 was measured. A third measurement D3 was taken at T3, 45 sec after T2. If D2 or D3 was reduced 50% or more, measurements were continued at 1 min intervals. Jaw stiffness Ki, the rotational resistance to mouth opening under an applied test moment M, was calculated following the formula:

$$Ki = M \cdot (2 \cdot \emptyset)^{-1} = F \cdot L \cdot (2 \cdot \sin^{-1}(Di \cdot (2 \cdot L)^{-1}))^{-1}$$

where M equals the applied test moment (F*L) about the TMJ, Ø is the half angle of mouth opening from fully closed position; F is the constant test force; L is the distance in the parasagittal plane from the condyle of the TMJ to the edge of the central maxillary incisors; Di is the maxillary-mandibular central incisal distance. Statistical analysis included analysis of variance (ANOVA), two-factor repeated measures ANOVA (RM-ANOVA), one-population RM-ANOVA (op-RM-ANOVA), analysis of covariance (ANCOVA) and the Mann-Whitney U test before and after logarithmic transformation.

Mean mouth opening Di in mm before and after relaxant administration

Relaxant	D1	D2	D3
Suc (n=22)	16.9 ± 2.8	12.6 ± 4.3*	13.0 ± 4.3*
Vec (n=21)	19.8 ± 3.6	20.4 ± 4.0 ⁺	20.9 ± 4.1
ANOVA	F≃8.6 P<0.006	F=37.1 P<0.0001	F=37.5 P<0.0001

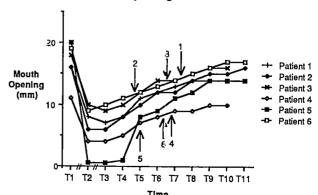
Indicates intra-subject, within-group differences significant at the P<0.0001 (for D2) and at the P<0.0005 (for D3) level by the one-population repeated measures ANOVA.

Results: The group of patients receiving succinylcholine (N=23) did not differ significantly from the control group receiving vecuro-nium (N=22) except for D1 and K1 (ANOVA). One patient's mouth opening reduced to less than 1 mm after succinylcholine, resulting in a large standard deviation. The statistical analysis is, therefore, given without this outlier (table). The RM-ANOVA for mouth opening demonstrated a significant (P<0.0001) interaction between the relaxants and the repeated measures of Di. With each subject serving as his own control within groups (op-RM-ANOVA), mean mouth opening reduced significantly, 4.2 mm at T2 and 3.9 mm at T3 and opening reduced significantly, 4.2 mm at 12 and 3.9 mm at 13 and mean jaw stiffness increased to 154 Nm/degree (P<0.01) at T2 and 150 Nm/degree (P<0.02) at T3, after limb relaxation with succinylcholine. In contrast, patients receiving vecuronium developed a significant increase in mouth opening at T3. Between group comparisons of D1, D2, D3, D2-D1, D3-D1, (D1-D2)/D1, and (D1-D3)/D1 demonstrated significant differences between relaxants by ANOVA and Mann Whitney U analyses, also after logarithmic transformation (table). ANCOVA, with D1 as covariate, confirmed the D2, D3, D2-D1, and D3-D1 differences. Jaw stiffness analyses confirmed the mouth opening results. Six patients in the succinylcholine group reduced their mouth opening 50% or more. Changes in mouth opening over time are shown in the figure. Their mouth opening remained reduced beyond the time at which the first visible twitch returned (arrows). As recovery from limb relaxation progressed, mouth opening returned towards baseline values. Increased masticatory muscle stiffness was observed for up to 10 min. Two of these pat ents required multiple attempts at intubation due to mouth opening reduction. Enflurane anesthesia, usually in excess of one hour, was continued throughout the procedure without signs of hypermetabolism or hyperthermia.

Discussion: Significant reductions in mouth opening and increases in jaw stiffness were demonstrated after succinylcholine but not after vecuronium administration, at a time when full relaxation of the limb muscles was present. The increases in masticatory muscle stiffness following succinylcholine during limb flaccidity suggests a property of the mast catory muscles fundamentally different from those of the limb musculature. The reduction in mouth opening and the increase in jaw stiffness following succinylcholine during deep enflurane anesthesia may represent the usual pharmacological response of the masticatory muscles. Thus, endotracheal intubation may not be facilitated following succinylcholine during deep enflurane anesthesia. Furthermore, "strong responders" in terms of magnitude and duration (isolated "masseter spasm") may be one end of the distribution of this response in the normal population.

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Mouth Opening versus Time



⁺ Indicates intra-subject, within-group differences significant (p<0.05) by one-population repeated measures ANOVA.

Title: HEMODYNAMIC AND HORMONAL EFFECTS OF ALFENTANIL AND MICAZOLAM IN DOGS

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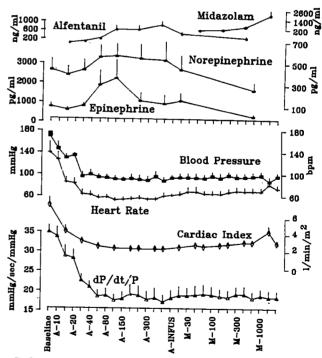
Introduction. High dose morphine was introduced into anesthesia because in the doses used it has no direct negative inotropic cardiac effects. The same property is shared by the newer, more potent, opioids. Nevertheless, it is well documented that decreases in hemodynamic function have been encountered with narcotic analgesics,1 especially in combination with benzodiazepines.² These occurrences have been ascribed to a decrease in central sympathetic outflow when sympathetic tone was needed to maintain homeostasis.³ A fall in plasma catecholamines (CA) has been reported to parallel hemodynamic changes in both patients and animals.^{2,4} Plasma norepinephrine (NE) levels are widely, though not unanimously, accepted indicators of sympathetic efferent activity.⁵ 28 We report here that alfentanil (ALF), unlike fentanyl, did not lower systemic plasma CA in dogs, although it did cause decreases in hemodynamic function. CA levels fell only when midazolam (MID) was added.

Methods. Mongrel dogs were anesthetized with 80 mg/kg alpha chloralose, intubated and ventilated with 66% N₂O in oxygen to normal end-tidal pCO₂. The animals were instrumented to measure arterial pressure (AP), ECG, heart rate (HR), and left intraventricular pressure, which was used to derive dP/dt/P. When desired, cardiac output was measured by thermodilution in triplicate, and arterial blood samples obtained. Femoral veins were used for administration of fluids (4ml/kg/hr) and of drugs in stepwise, increasing, cumulative doses. Plasma CA were determined by HPLC; ALF and MID by GC. Intragroup data was analyzed by ANOVA followed by the Bonferroni modified t-test. Statistical t-test. Statistical significance was assumed at p < 0.05.

Results. The figure shows the stepwise fall in AP, HR, CI, & dP/dt/P with 10, 20, and 40 ug/kg of ALF. Higher doses of ALF followed by an infusion had no additional effects. Plasma CA showed no change at the lower 2 doses and rose with the nigher ones. MID up to 0.3 mg/kg had no nemodynamic effects; a belus dose of 1 mg/kg aused only a transient drop in AP and increases in HR and CI. Plasma CA at this time were below control levels. Glycopyrrolate pretreatment in a separate group of dogs, in doses sufficient to ncrease HR maximally, failed to alter the AP, CI, or dP/dt/P. HR drop was small and brief. In a third which were autonomically eries of dogs, lenervated, the same drug doses given in the same vay caused no changes whatever.

<u>Discussion</u>. These results with ALF clearly differ rom the earlier ones with fentanyl in which CA ell together with hemodynamics 4 The main aethodological difference is the anesthesia. Alpha hloralose is well known to preserve reflexes and naintain high sympathetic tone compared to the nflurane-N₂O anesthesia used in the fentanyl xperiments. This difference alone does not explain

the discrepancy between hemodynamic and plasma CA changes. Plasma NE, even in arterial blood, only reflects the balance between the transmitter overflow during sympathetic nerve activity, which amounts only to a small fraction of the amount released, and the clearance rate. If a drug reduces neurogenic NE release but increases the percent reaching the systemic circulation, and/or decreases other clearance mechanisms at the same time, there would be no change or even an increase in the plasma concentration measured. Methods to measure CA clearance are available, but have not been applied to the issue under discussion, nor have measurements of drug effects on NE overflow been done. Furthermore, sympathetic tone, predominant in determining cardiovascular function, is certainly not the sole factor. A parasympathetic mechanism has been ruled out by the glycopyrrolate observations.



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Title: HALOTHANE MAG IS STEREOSPECIFICALLY REDUCED BY MEDETOMIDINE, AN ALPHA₂ AGONIST

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Introduction: Clonidine, the alpha2 adrenergic agonist, reduces the dose requirements for anesthesia and analgesia during surgical stimulation 1,2 Unfarements . Unfortunately, a "ceiling effect" followed by a reversal of the initial effect is obtained at higher clonidine doses and may limit its efficacy as an adjunctive agent for general anesthesia. Medetomidine is more selective as a full agonist for central alpha₂ adrenoceptors than is clonidine⁴, is well-tolerated by patients⁵ and is also available as individual stereoisomers. We now report on the MACsparing and cardiovascular effects of the stereoisomers of medetomidine in halothaneanesthetized dogs.

Anesthesia was Methods: induced by inhalation of halothane in oxygen in seven male teagles (8-11 kg). Following tracheal intubation mechanical ventilation was initiated, to maintain normocarbia. Catheters were inserted percutaneously for intraarterial pressure recording (femoral artery), for pulmonary arterial and central venous pressure monitoring and cardiac output assessment (thermodilution) and for intravenous fluid and drug End-tidal administration. halothane concentrations, heart rate and rhythm, systemic arterial pressure, central venous pressure pulmonary and arterial pressure were continuously displayed and recorded. Core temperature was maintained at 37°C with a heating pad. After a 2 h equilibration period, the MAC for halothane was determined and baseline hemodynamic function was assessed. DL-Medetomidine, at 3 doses (1, 3 and 10 $ug \cdot kg^{-1}$) was administered via the right atrial port over 5 min while maintaining the dog at its individual MAC for Ten min later, hemodynamic parameters were reassessed. MAC determination was then repeated. In two separate sets of experiments, dogs (n=5 each) were administered either the D or the L enantiomer of medetomidine and the same procedure followed as described above. Data were compared by ANOVA for repeated measurements and subsequently by paired t-test with Bonferroni correction. A p value of < 0.05 was considered the level for significance.

Results: MAC for halothane significantly decreased following DL-medetomidine administration in a dose-dependent fashion. The D-isomer displayed the same MAC-sparing effect as the racemic mixture while the L-isomer was without effect (Fig 1).

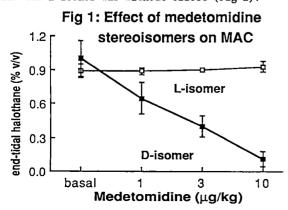


Fig 3: Effect of medetomidine stereolsomers on cardiac output

L-isomer

D-isomer

D-isomer

Medetomidine (µg/kg)

Neither isomer changed the mean arterial pressure while only the Disomer significantly decreased heart rate (Fig 2) and cardiac output Discussion: Medetomidine, the highly selective alpha2 adrenergic agonist, reduces MAC for volatile anesthesia by a degree greater than with any o t h e r physiologic, pharmacologic, or pathologic intervention thus far reported. The fact that this effect is stereospecific suggests structure activity

relationship that can be accounted for by a homogeneous receptor population. Both prepostsynaptic alpha2 adrencceptors may mediate this former the response, by inhibiting noradrenergic neurotransmission and the latter by an as yet undescribed mechanism which is currently under investigation in our laboratory. The reduction in cardiac output following medetomidine may be due to one or more of the following: 1) bradycardia; 2) postsynaptic alpha2 mediated vasoconstriction of the peripheral vasculature; and 3) decreased oxygen requirements with the increasing depth The role of medetomidine anesthesia. supplemental anesthetic agent appears promising and requires further investigation.

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<u>Acknowledgements:</u> The authors gratefully acknowledge, Dr Risto Lammintausta, for supplying medetomidine and the IARS for supporting this study.

Title: CAN TRANSESOPHAGEAL ECHOCARDIOGRAPHY PROVIDE USEFUL INFORMATION IN REAL TIME IN THE OPERATING ROOM?

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Introduction: Transesophageal two dimensiona echocardiography (TEE) provides a reproducible assessment of global and regional left ventricular (LV) function. The development of new regional wall motion (RWM) abnormalities was shown to be a sensitive and early marker of myocardial ischemia in patients having cardiac surgery. However, this study and many others employing TEE intraoperatively, have utilized retrospective analyses of videorecordings. They were not performed in real time, on-line, in the operating room, and therefore the clinical utility of TEE was not assessed. In this study we evaluated an anesthesiologist's ability to accurately assess RWM on-line intraoperatively.

Materials and Methods: The study was approved by the Institutional Review Board and informed consent was obtained from each patient. Fourteen patients undergoing cardiac surgery were studied (13 males and 1 female; mean age of 66). Nine patients underwent coronary artery bypass grafting (CABG), 3 patients underwent aortic valve replacement for aortic stenosis and 2 patients had combined CABG and aortic valve replacement. The anesthetic regimen consisted of a narcotic base supplemented with a volatile anesthetic agent. provided a view of the 5 LV segments (inferior, inferoseptal, anteroseptal, anterior and lateral) visible at the midcavity level. At 4 designated times during the course of the operation (pre-incision, post-sternotomy, post-protamine and at skin closure) an on-line assessment of RWM was made by an anesthesiologist (MDA). Each segment was scored by estimating wall thickening (SWT) and endocardial motion (SEM) during systole as follows: (1)=normal SWT and SEM Hypokinetic (2)=moderate reduction in SWT and SEM (3)=minimal to absent SWT and SEM Akinetic Dyskinetic (4)=paradoxical SEM and/or SW thinning At a later time, utilizing videorecordings obtained at the 4 time periods, cardiac cycles representing each period were digitized and displayed on a quadscreen (Microsonics computer) to facilitate RWM analysis by an experienced echocardiographer (RN). Data obtained on-line were then compared with the computer-assisted analysis which were considered to be the reference standard.

Results: In the interval from pre-incision to skin closure, 65% of segments remained unchanged, 24% of segments deteriorated, and 11% of segments improved. Sixty-five percent of RWM changes noted were in the septal region. Figures 1 and 2 show the correlation between the on-line assessment of RWM as compared with the analysis done by an echocardiographer. There was complete agreement of RWM score in 68% of segments analyzed (187/275) and disagreement by two or more grades in 5% (14/275) segments analyzed (Figure 2). Of the 88 disagreements in RWM analysis 51 (58%) were in the septal segments.

myocardial ischemia, it is uncertain whether subtle changes in RWM can be reliably detected intraoperatively so as to affect a change in management. In this study, there was generally good agreement in RWM score between the real time and retrospective analysis. Nearly 60% of differences in RWM score occurred in the septal segments. Of concern are discrepancies of more than 2 grades seen in 5% of RWM analyses. Charges in RWM in the septal segments have been reported to occur after cardiac surgery and may be related to pericardiotomy with a loss of pericardial "tethering", and not necessarily due to ischemia. 3 Other possible causes for discrepancies in RWM assessment include differences in segment demarcation, the inability to make on-line comparisons of the echocardiograms obtained at sequential time periods and differences in the interpretation of RWM.

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Figure 1
Regional Wall Motion Analysis: Real Time vs
Computer Assisted Retrospective Analysis

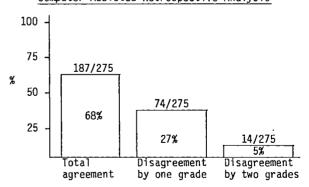


Figure 2
Computer-Assisted Retrospective Analysis of RWM

		1	2	3	4
Intraoperative	1	157	26	3	0
Real Time	2	20	24	21	1
Analysis of RWM	3	3	1	6	0
-	4	0	7	6	0

275 segments out of a possible 280 segments were scored. 5 segments could not be assessed.

OXYGEN SATURATION IN CHILDREN FOLLOWING ADMINISTRATION OF RECTAL METHOHEXITAL

Authors:

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Introduction. Rectal methohexital (Brevital) is an induction agent commonly used to facilitate separation of small children from their parents. 1 Although this technique has been used with apparent safety in many patients, effects upon oxygenation are unknown. This study was designed to evaluate the effect upon oxygen saturation of rectal methohexital.

Methods. Patients ranging in age from 8 months to 5.5 years were selected at random. All were ASA I or II without cardiopulmonary disease. Oxygen saturation and heart rate values were recorded with a Nellcor pulse oximeter placed on a digit prior to administration of rectal methohexital. The dose of methohexital was chosen by the anesthesiologist. Recordings were made every 30 seconds of oxygen saturation, heart rate, state of consciousness and body position and were continued until the patient was transported to the operating room. Since many patients were carried, recordings were resumed when the patient was placed on the operating table.

Results. Twenty-four patients were studied. Eleven were cooperative enough to enable accurate recording of oxygen saturation prior to administration of methohexital. One dose of methohexital was given to each child (24-34 mg/kg.) Twenty-two patients went to sleep with this dose; two were mildly sedated but separated easily from their parents. Ten of the 24 patients developed an oxygen saturation less than 95% after methohexital administration. In 4, saturation was less than 9 (range 81-89%.) The table illustrates when these In 4, saturation was less than 90% desaturations occurred. Four patients developed desaturation in the holding area. Of these, 1 Datient desaturated to 81% while crying and upset but this abated spontaneously as sleep occurred. Desaturations seen in the other 3 patients also resolved spontaneously. In 7 patients, desaturation was described following transport with the first measurement taken on the operating table and all resolved with supplemental oxygen. One of these

patients also desaturated in the holding area. Cyanosis, airway obstruction or heart rate less than 100 b.p.m. were not appreciated in any patient. Position in the holding area or during transport did not correlate with desaturation.

<u>Discussion</u>. Our results demonstrate that oxygen desaturation commonly occurs following induction with rectal methohexital. Pulse oximetry can detect this non-invasively in the absence of clinical signs. Desaturation that occurs in the holding area prior to transport appears to be self-remitting. Desaturation more commonly occurs after sleep following transport to the operating room. Therefore, following rectal methohexital, patients should not be left unattended, they should be transported expeditiously, and supplemental oxygen should be readily available.

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TABLE

	<u>0xygen</u>	Saturation
# of nationts with	90-94%	80-89%
# of patients with desaturation in the holding area	2	2
# of patients with desaturation upon arrival in the O.R.	4	3

COMPARATIVE ANALGESIC EFFICACY OF EFIDJRAL NALBUPHINE, BUTORPHANCL, MEPERIDINE AND MORPHINE

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INTRODUCTION. Epidural administration of morphine rovides profound analgesia but also causes adverse ffects. 1 Much interest has been focused on finding suitable replacement for epidural morphine. The resent study was undertaken to evaluate the analgeic efficacy and safety of epidural nalbuphine and utorphanol, two widely used partial agonist-antagoist opioids, in comparison to that of epidural mor-

hine and meperidine.

METHOD. The study was conducted after instituional approval and informed consents were obtained rom all the patients prior to their entry into the tudy. Eighty adult patients scheduled for elective pper abdominal surgeries were enrolled in this stucy. n the day of surgery, prior to induction of anesthe-ia, an indwelling #18 gauge epidural catheter was nserted through the L₁₋₂ or L₂₋₃ lumbar vertebral nterspaces and taped securely in place. All the patents were then given general anesthesia with either alothane or enflurane in N₂O-O₂ without any national callegic. In the post on posicial when the patents. nalgesic. In the post-op period, when the patients illy recovered from the effect of anesthesia and omplained of severe pain, they were divided into 4 qual groups of 20 patients each in a randomized, puble-blind fashion and received epidural administraion of meperidine 50 mg (group 1), butorphanol 2 mg group 2), nalbuphine 10 mg (group 3) and morphine alfate 5 mg (group 4) respectively. All medications are prepared in 10 ml normal saline. All patients ere observed for pain relief (by visual analogue cores), vital signs, arterial blood gas studies and lverse effects for 24 hours. "Rescue" analgesics of peridine 50-75 mg I.M. were given whenever patients implained of recurrence of severe pain.

The demographic distribution and initial in intensities were similar for all 4 groups. Onse-pain relief with epidural nalbuphine and butorphaappeared at 5-10 minutes, peaked at 25-30 minutes th a duration averaging 6.4 hours, and 6.2 hours spectively. Epidural meperidine showed a similar algesic onset with a longer duration of action eraging 8.3 hours. On the other hand, onset of algesia with epidural morphine began at 15 minutes. aked at 60 minutes, and lasted 16.2 hours (Fig). cidence of adverse effects were much less in the idural nalbuphine and butorphanol groups (Table I) clinically significant respiratory depression was served in any of the patients but PaCO2 values for e butorphanol and morphine groups were increased er baseline values at different time periods (Table

DISCUSSION. In our study both epidural nalbuphine d butorphanol demonstrated a very similar analgesic ofile with faster onset and shorter duration of tion compared to that of morphine. The rapid onset d short duration probably is due to their high lid solubility which also accounts for the short tion of epidural meperidine. Being primarily Kappa onist both nalbuphine and butorphanol were associed with less incidence of adverse effects commonly served with epidural morphine. Even though no paent showed clinically significant respiratory deession (respiratory rate <10/min.) arterial blood s studies did show statistically significant ineases in PaCO2 in the butorphanol group at 30 min.,

1 and 2 hours post drug administration (P < 0.05). Our observation is in accordance to that reported by Rein, et al.² In conclusion, epidural nalbuphine and butorphanol appear to provide efficacious pain relief with less untoward effects in patients with postoperative pain but their analgesic effects might be too short to make them an ideal replacement for epidural morphine for this purpose. REFERENCES.

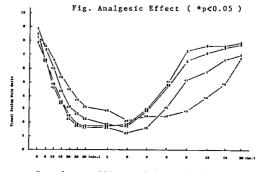
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TABLE 1 SIDE EFFECTS

	Grp.1	Grp.2	Grp.3	Grp.4
Nausea	15%	15%	10%	30%
Vomiting	10%	5%	5%	20%
Pruritis	10%	0	0	20%
Drowsiness	55%	50%	15%	20%
Urinary Retention (in non-catheterized pt.)	40%	40%	35%	70%
Respiratory depression	0	0	0	0

TABLE 2 PaCO₂ VALUES (*P < 0.05) Hour 0 Я Group 1 38.6 40.0 39.7 38.0 38.5 37.8 +5.2 ±7.1 ±6.1 ± 5.0 ± 5.7 ± 5.7 2 37.4 42.4* 40.5* 39.3* 38.4 38.5 ±4.8 ±6.0 ±5.8 <u>+</u>4.3 ±5.4 ±5.1 3 37.7 37.9 38.4 38.5 37.6 37.8 +2.5 <u>+</u>2.9 ±3.0 ±2.9 ± 2.6 +3.0 38.1 38.4 39.0 40.6* 39 7 38.0 ±2.8 +2.9 <u>+</u>2.6 +3.4±2.9 +2.9



Grp. 1=meperidine 3=nalbuphine

2=butorphano1 4=morphine

CHANGES IN PULMONARY VASCULAR IMPEDANCE OF HEART TRANSPLANT RECIPIENTS AFTER Title:

CARDIOPULMONARY BYPASS

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Cardiopulmonary bypass (CPB) is Introduction. followed by a transient increase in pulmonary vascular impedance (PVI) among patients with normal preoperative pulmonary circulation. Thus, heart homografts, whose right ventriclar function is dependent on PVI2, may by adversely affected after The purpose of the study was to determine the effects of CPB on total pulmonary vascular resistance index (TPVRI), a measurement of PVI in heart recipients after CPB.

23 heart transplant recipients (NYHA Class IV) with cardiomyopathy (PCM, n=11) or ischemic cardiomyopathy (ICM, n=12) (males 20, females 3; 52 ± 13 yrs, 72 ± 13 kg, $1.8 \pm .2$ m² BSA) were premedicated with Torazepam (10-30 mcg/kg) anesthepremedicated with Torazepam (10-30 mcg/kg) anesthetized with fentanyl (25 + 19 mcg/kg) and isoflurane (.25-.75%) in oxygen and air (Fi02 \geq .7), paralyzed with vecuronium (.1 mg/kg) and mechanically ventilated (PaCo2 33 \leq mmHg, PEEP = 5 cm H20). Drug support before or after CPB included dobutamine (DBT), dopamine (DOP), isuprel (ISU), nitroglycerin (NTG) or nitroprusside (NTP), (mcg/kg/min), to maintain cardiac index (CI) \geq 2.5 L/min/m² BSA. After heparinization (300 units/kg) hypothermic (28°C) CPB (plasmalyte®-mannitol prime) was initiated (Q = 1.8 L/min/m² BSA, MAP 70 mmHg, hematocrit \geq 25%). Isoflurane (.25-1%) was vaporized in the oxygenator to control MAP and assure amnesia. Heart rate (HR, bpm), mean aortic pressure (MAP, mmHg), mean pulmonbpm), mean aortic pressure (MAP, mmHg), mean pulmonary artery pressure (MPAP, mmHg), central venous pressure (CVP, mmHg), pulmonary artery diastolic pressure (PADP, mmHg), thermodilution cardiac index (CI, L/min/ m² BSA), systemic and total pulmonary vascular resistance indices (SVRI, TPVRI and PVRI [Normal=350 \pm 80], dynes sec cm⁻⁵m² BSA) were measured at steady state and/or calculated (standard equations(3)) within 20 minutes before and after CPB. CPB (CPBT), graft ischemia (IT), and reperfusion times (RT), FiO₂, PAO₂ (mmHg), (A-a)O₂ (mmHg), Hct, ABG, Temp (°C), electrolytes, anesthetic and vasoactive agents were recorded at the time of hemodynamic measurement. Student t test and Pearson regression analysis (EPISTAT®) were used to establish lish significance and correlation.

Results. In 8 of 23 patients (Group I: ICM 5, PCM $\overline{3}$) TPVRI rose 21% from prebypass values of 530 \pm 193 (p < .05) while in the remaining 15 (Group II: ICM 7, PCM 8) TPVRI decreased 33% from prebypass values of 735 \pm 310 (p < .01) (Figure). Group I and II were matched, before bypass, for age, wgt, BSA, diagnosis mixture, HR, MAP, CVP, CI, SVI, TPVRI, SVRI, pH, PCo₂, P_AO₂, A-aDo₂, DOB, DOP, NTG, NTP and inspired isoflurane and fentanyl dose. MPAP and PADP before bypass were lower in Group I (23 ± 6, 17) +5) than in Group II (31 + 9, 25 + 7) respectively (p = .02), and postbypass decreased (MPAP 17%, PADP 16%) only in Group II (p = .02). For all patients percent change in TPVRI postbypass was a linear function of the percent change in PADP (Y = .74X-8.5, p < .01, R = .63). Although CBPT (143 + 48, 122 +

21), IT (154 \pm 58, 163 \pm 66) and RT (63 \pm 36 vs 53 \pm 14) of Group I and II respectively were not different, post bypass CI and SVI of heart homografts were higher in Group II (4.5 \pm 1.2, 41 \pm 14) than in Group I (3.2 \pm .5, 30 \pm 7, p < .05) for similar postbypass HR (Group I 109 \pm 11 and Group I 114 \pm 22) II 114 \pm 22). For both groups, heart homograft CI was a linear function of postpypass TPVRI (Y = 6.57 was a linear function of postbypass TPVRI (Y = 6.57 -4.7X, p < .001, R -.72). SVRI was significantly lower in Group II (1004 + 271) than in Group I (1633 + 209), p < .01. After bypass pH and pCo2 were similar but, Hct was 36% lower (hemodilution) and PAo2 and (A-a)o2 (Fio2 = 1.0), were 34% and 39% (Group I and II) higher than prebypass values in both groups with no differences between groups. Post bypass rates of administration of DBT (7 + 3, 6 + 4), DOP (1 + 2, 1 + 1), NTG (3 + 2, 3 + 1), NTP (3 + 2, 3 + 2), for Group I and II respectively were not different between groups. ISU (.01 + .02, .02 + 03) was given only after bypass. Rates of .02 + 03) was given only after bypass. Rates of NTG, NTP were higher after than before bypass (1+1,

<u>Discussion</u>. The reported increase in PVI after CPB occurred in only 1/3 of heart transplant recipients. In the remaining 2/3 of recipients, we recorded a significant fall in PVI. These opposite changes in PVI may reflect the difference in performance of each group's respective left ventricles rather than changes in pulmonary vasculature. This difference in left ventricular performance which can be explained by differences in SVRI may also be reflected in the respective PADP, which in this study correlated well with changes in TPVRI.

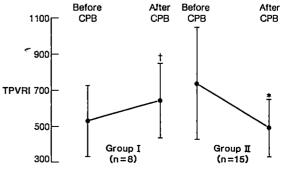
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Transplant Proc 3:337, 1972.
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*p <.001 (Paired T-test) Significantly different from before CPB †p <.05 (Paired T-test) Significantly different from before CPB

TITLE:

DOES AGE AFFECT USE OF THE PRIMING PRINCIPLE FOR RAPID INTUBATION?

AUTHORS:

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INTRODUCTION: The utility of the priming principle for speeding onset of muscle relaxation remains controversial. This may be because the optimal loses and time intervals between doses required in lifferent circumstances are not known. This study compares different time intervals between fixed rriming and intubating doses of vecuronium in a oung and geriatric population. ETHODS: With institutional approval, 65 PS 1-3 surgical patients were studied. Forty two patients were 18-40 years old (Group A), and 23 were greater han age 65 (Group B). Fentany1 50-200 ug iv, and idazolam 1-3 mg iv, was administered as necessary o allow awake neuromuscular blockade monitoring. he ulnar nerve was stimulated supramaximally with epetitive trains-of-four (2 Hz for 2 sec at 10 sec ntervals) at the wrist with surface electrodes. he evoked compound electromyogram of thumb dduction was obtained using the Puritan-ennett/Datex Neuromuscular Transmission Monitor. he degree of neuromuscular block was described as ercent of control of the first train-of-four esponse. Each patient was randomly assigned to one f 5 cells comprising the Group. Cell 1 patients eceived a single dose of vecuronium 0.1 mg/kg iv fter induction of anesthesia. Patients in cells -5 received a priming dose of vecuronium 0.01 mg/kg v prior to anesthetic induction, followed by 0.1g/kg iv after the assigned interval (2,4,6,and 8 in, respectively). Prior to administration of the econd dose (or single dose), anesthesia was induced ith thiopental 3-5 mg/kg iv and fentanyl 100-500 ug v, and maintained with nitrous oxide/oxygen. No platile anesthetics were administered. Intubation is attempted 90 sec after the single or second dose f vecuronium. Per cent twitch depression just cior to the second dose, per cent twitch depression) sec after second dose, and time to 95% blockade is recorded for each patient. An ease of ntubation score ranging from 4 to 1 (easy, some esponse, difficult, impossible - respectively) was ssigned to each patient. Symptoms of weakness fter administration of the priming dose were ecorded. Statistical analysis of twitch height and set time data was done by analysis of variance, ne Student-Newman-Keuls test, and t-test. itubation scores were analyzed by the Kruskalillis test. SULTS: Patients in Group A averaged 30 +/- 7.6

SULTS: Patients in Group A averaged 30 +/- 7.6 pars of age (mean + SD), while Group B patients reraged 71 +/- 5.3 years of age. No patients affered significant side effects due to the priming see. Twitch depression prior to the second dose as minimal in all cases. Group A patients showed a gnificant increase in the degree of twitch pression 90 sec after the second vecuronium dose, presponding to increases in the dose interval from to 8 min (p<0.05) (Table). Significant fferences were found in the times required for 95% ock (Table). The cell that received a single tubating dose took significantly longer to achieve

95% block than the 6 min priming interval cell or the 8 min cell. The group using a 2 min interval also took significantly longer than the 8 min group. There is insufficient data at this time to perform a similar analysis of variance for Group B (age > 65).

Comparison of the single dose cells for young and old showed a longer time to 95% block for the older group (p<0.05). Comparing the $8\ \mathrm{min}$ interval cells also showed a longer time to 95% block for the older group (p<0.05). The difference for the 6 min interval cells was suggestive of a longer time to 95% block in the older group. Evaluation of intubation scores in the younger group showed that priming intervals of 2, 4, 6, and 8 minutes all provided significantly easier intubating conditions than single doses of vecuronium. Insufficient data exists for similar analysis in the older group. CONCLUSION: This study shows that priming with vecuronium effectively achieves rapid twitch depression and good intubating conditions when used in young patients. 6 minutes was found to be an adequate priming interval when doses of 0.01 mg/kg and 0.1 mg/kg were used for priming and intubation in this age group. The data obtained suggests that priming may expedite relaxation in old patients. However, times to 95% twitch depression are longer in this group when compared to young patients even when the same doses and time intervals are used.

These findings suggest: 1) priming is effective in young people, 2) using accepted doses and intervals (1), priming may not be sufficiently effective in geriatric patients to be considered a safe technique for rapid intubation, 3) appropriate doses and intervals for older patients should be sought in appropriately designed studies, not inferred from data obtained from younger age groups. TABLE $(\text{Mean } +/-\text{SD}) \qquad *= p < 0.05$

	GRP 1A 1B	<u>n</u> 8 5	<u>I</u> single dose	<u>II</u> 57+/-28 20+/-37	<u>III</u> 156+/-47 * 242+/-85
	2A 2B	6 7	2	57+/-29 47+/-29	142+/-43 170+/-44
	3A 3B	9 2	4	67+/-33 45+/- 6	129+/-40 200+/- 0
	4A 4B	9 5	6	83+/-19 70+/-39	101+/-28 125+/-70
. 1	5A <u>5B</u>	10 4	minutos)	83+/-19 59+/-17	101+/-28 * 170+/-69

I: Priming interval (minutes)
II: Twitch depression 90 sec after 2nd dose of VEC
III: Time to 95% blockade (seconds)

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ANESTHETIC CONSIDERATIONS IN PATIENTS WITH CARDIAC PACEMAKERS Title:

UNDERGOING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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Introduction. In extensive in vitro studies 7 % of all tested single chamber pacemakers (SCPM) and 67 % of dual chamber pacemakers (DCPM) showed shock wave (SW) induced dysfunctions due to electromagnetic and mechanical interferences (1). Even complete mechanical failure has been described when the pacemaker (PM) has been exposed to the focal point of the shock wave (2). Therefore, extracorporeal shock wave lithotripsy (ESWL) has been considered an absolute contraindication in the presence of a cardiac PM. On the other hand, in vitro tests demonstrated that PM-malfunctions can be avoided by adequate safety measures such as reprogramming a DCPM into a single chamber mode (VVI).

Methods. After obtaining Institutional Review Board approval and informed consent, eleven ASA class III or IV patients (7 males and 4 females; age 47 - 74 years) with cardiac pulse generators and nephrolithiasis underwent ESWL-treatment under general anesthesia using a Dornier HM 3 - Lithotripter (Fig. 1). 7 patients with a SCPM (Medtronic 5983, CPI 522, Pacesetter 221 A, 2 x Cordis 337 A, 2 x Biotronic Neos O1) and 2 patients with a DCPM (Pacesetter AFP 283, Medtronic Versatrax 7000) were included in the study and all PMs were located in the pectoral region. In 2 patients a temporary external PM was used (2 x Medtronic 5375). All pulse generators were checked before and after treatment. During ECG-synchronized SW-application stability of programming, threshold, pacing and sensing functions were tested. Mode of operation, stimulating rate, sensitivity and amplitude of the pulse generators were varied. Synchronous recording of shock waves, ECG and arterial pressure allowed exact analysis of the shock wave triggering event and the possible hemodynamic consequences (Fig. 2).

Results. An average of 1200 SWs (range 500 - 1700) at an energy level between 16 and 20 kV was applied during each treatment. Initially, all PMs were set to single chamber mode (VVI). No SW-related malfunctions could be detected under these conditions. Even after switching to other modes of operation (AAI, VAT, DVI, DDI, DDD) in the 2 patients with a DCPM, no changes in sensing and stimulating, or disturbances of programming could be observed. Analysis of time intervals in the ECG-recordings proved that in all cases SWs were released by the PM-initiated QRS-complex and never by the PM-spike itself, thus avoiding SW-induced arrhythmias (Fig. 2). The minimal distance between PM and SW-axis was 11 cm. The distance between PM and calculus measured at least 16 cm.

Conclusions. This clinical study demonstrates that ESWL in cardiac pacemaker patients is a safe procedure, provided the following key safety measures are applied:

- 1) Pre- and post-treatment control of PM-function.
- 2) Availability of the type-specific PM-programmer.
- 3) Modification of the PM-programming (low atrial sensitivity and prolonged refractory period) according to ESWL conditions.
- 4) SW-triggering only by QRS-complex, not by PM-stimulus (depending on quality of signal processing

- in the ECG-monitor).
- 5) Evaluation of the distance PM to SW-axis with special consideration for abdominally implanted PMs (Fig. 1).
- 6) Insertion of a large central venous access capable of holding a pacing lead.

Results of this study cannot be extended to other types of lithotripters and newer high-sensitive PMs such as rate responsive systems.

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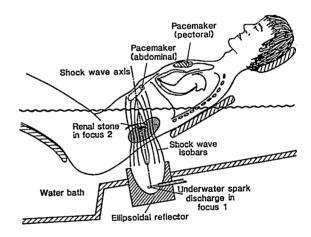


Figure 1. Patient positioning in the lithotripter (note the spatial relationship between shock wave axis and implanted pacemakers)

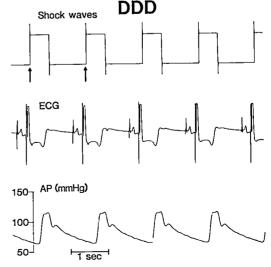


Figure 2. Original recording of QRS-complex-triggered shock wave impulses (arrows), ECG and arterial pressure (AP)

HEMODYNAMIC STUDY OF EPIDURAL CLONILINE IN AWAKE SHEEP

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Introduction. Increasing evidence suggests that epidurally applied alpha-2 agonists (eg clonidine) may produce analgesia by a mechanism different than that of narcotics (1). Before epidural administration of clonidine for pain control in humans can be evaluated the hemodynamic safety of this route must be ensured. This study was designed to answer three related questions concerning; 1) the hemodynamic consequences of epidural clonidine in awake sheep, 2) the time course for the hemodynamic effects of epidural clonidine, and 3) whether there is a mechanism to correct any hemodynamic changes produced by the drug given by this route.

Methods. As approved by the Animal Resources Centre, 6 non-pregnant breeding-age sheep, weighing 50-90 kilograms, were prepared under halothane anaesthesia. Regional dissection allowed insertion of a right carotid arterial line, a right internal jugular Swan-Ganz catheter, and a percutaneous lumbar epidural catheter. Placement of these lines was cmarfirmed by hemodynamic measures for the arterial and Swan-Ganz catheters and radiographically for the epidural catheter.

The sheep were allowed to recover for 24 hours and remained stable during the study period. Over the next 3 to 5 days the response of these unsedated mimals to an increasing dose of clonidine, given in 5 mls of saline through the epidural catheter, was recorded. On the first day 5 µg/kg was given; and the next, 10 µg/kg; and on the third, 15 µg/kg. Dentral venous pressure (CVP), heart rate (HR) and cardiac output (CO) were recorded as a base line and to 15, 30, and 45 minutes after each dose. Forty—live minutes after the largest dose the changes in XP and HR were corrected with crystalloid and tropine sulfate and the hemodynamic measures were repeated. Statistical analysis of data was performed using the Wilcoxon signed rank non-parametric test.

Results. The decreases in HR and CO were less tarked with increasing dose and time. These results gree with previous work done in anaesthetized pigs and dogs (2),(3). The CVP decreased constantly as ose and time increased. These changes, at all oses, were significant (P < 0.05) when compared to ontrol. Mean arterial pressure showed a tendency of decrease following the low doses and to increase fter the higher doses, but neither change was statistically significant. Systemic vascular resistance SVR) increased significantly (P < 0.05) after $0 - 15 \ \mu g/kg$. Restoring central venous pressure to

the baseline improved cardiac output, but only by correcting both CVP and HR could cardiac output be returned to normal. Table I. As CO was restored systemic vascular resistance returned towards baseline.

Discussion. The decreases in HR, CO and CVP may be related to decreased sympathetic output and changes in intravascular volume. The changes in HR and CO were less marked at the highest dose and at the end of 45 minutes, suggesting that near maximal depression had occurred. The CVP decreased in a linear fashion with dose and time. The correction in these three variables by infusion of crystalloid and atropine suggested no significant negative inotropic effect of epidural clonidine at these doses. This manipulation produced an increase in mean arterial pressure of 24% above baseline. This study documents a decrease in CO as a result of epidural clonidine in awake sheep. Dose and time response suggest a ceiling to this effect, while correction with volume and atropine suggest the mechanism to be a relative sympathectomy and drop in preload.

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Table I.

CARDIAC OUTPUT VS EPIDURAL CLONIDINE

CO @ 45 Min

					Cor	rected
	Control	5µg/kg	10µg/kg	15µg/kg	CVP	CVP + HR
CO/L	7.0	6.15	5.5	5.23	5.7	7.3
SE*	<u>+</u> .53	<u>+.49</u>	<u>+.43</u>	<u>+</u> .47	+1.26	+.65
2	100	88	79	74	81	104

* Standard Error

BARBITURATE-INDUCED ELECTROCORTICAL ACTIVATION FOLLOWING NARCOTIC-INDUCED EEG DEPRESSION

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Introduction. Several studies have described the predictable EEG depression that occurs when nar-cotics are used as induction agents. Caution must be exercised when interpreting EEG changes and correlating them with anesthetic state or depth especially when multiple drugs are used. We have investigated the EEG and hemodynamic changes that occur when small quantities of barbiturates are administered to patients anesthetized with narcotic induction techniques.

Methods. After obtaining informed consent and approval of the Human Investigation Committee, 23 ASA I and II patients with weights between 55 and 80 kg were studied. All patients were premedicated with glycopyrrolate and morphine 0.1 mg/kg IM at least 1 hour prior to anesthetic induction. Patients were monitored with automated blood pressure, EKG, pulse oximeter, nerve stimulator, and end tidal CO, monitoring. The Lifescan-Neurometric® EEG monitor and research system was used for monitoring electrocortical activity.

Following several minutes of baseline EEG and hemodynamic data collection, anesthesia was induced with vecuronium 0.05 mg/kg and fentanyl $12 \,\mu\text{g/kg}$ IV push. Patients were included in the study if a delta wave dominant pattern developed within three minutes of the fentanyl bolus and if the pattern remained stable for at least two minutes at which time EEG and hemodynamic data were again collected. The subjects were randomly assigned to one of two groups: Group 1 (N=9), patients received 6 cc of normal saline placebo IV, or Group 2 (N=10) patients received 2 mg/kg thiopental IV push. Two minutes later, EEG and hemodynamic data were again collected. During the induction period, motor responsiveness was tested using an isolated arm technique and two-word phrases were verbally introduced to the subjects to test for recall one day following surgery.

Results. Nineteen of the 23 patients achieved a stable delta wave dominant pattern. All patients were unable to respond to command and to spontaneously recall or recognize the phrases following development of the low-frequency high-amplitude delta dominant EEG pattern. Those patients remaining in an alpha dominant pattern, though heavily narcctized, were able to respond to command, spontaneously recall some phrases, and successfully recognized the other phrases.

The BP, HR, and EEG data are summarized in Table 1. Since baseline EEG activity, specifically the beta band, is frequently contaminated by significant amounts of EMG activity, the baseline EEG band percentages were calculated both with and without the beta band activity. EEG activity did not differ

between the two groups at baseline (A) and before placebo or barbiturate infusion (B). A significant increase in alpha and beta activity as well as a significant decrease in delta activity developed following administration of 2 mg/kg of thiopental (C) in Group 2.

TABLE 1

	· ·	Group 1 (N=5)	Gr	Group 2 (N-10)			
HR	A 74.2+11.7	B 67.8±13.4 68.6± 96.6±12.6 102.6±	A 8 8 8 8	B	C		
MAP	104.1 8.2	96.6+12.6 102.6+	14.5 39.5+12.7	96.5+11.3	32.8+ 7.8		
TP=D	+T+A						
ZD ZT ZA	12.1± 5.0 25.2± 8.3 62.6±11.1		9.3+ 5.4 21.8+ 5.8 58.9+ 9.6		j		
TP=D	+T+A+B						
		72.2+10.4 69.8+ 17.5+ 6.8 14.7+ 9.1+ 8.8 12.4+ 1.0+ 0.78 2.9+					
SEF 90%	20.1+ 3.2	5.8+ 2.5 5.95	+2.5	5.7+ 2.7	4.2+ 2.4		
	D = delta	power A = B = SEF =	beta	requency			

Discussion. Eighty-three percent of the studied patients receiving morphine premedication and 12 µg/kg fentanyl bolus achieved a stable delta wave dominant pattern associated with complete amnesia and probably unconsciousness. It is well known that small doses of thiopental produce electrocortical activation in awake resting subjects simultaneously with behavioral and cognitive depression. Barbiturate-induced depression of the medullary-pontine inhibitory output into the reticular activating system (RAS) presumably results in RAS activation and electrocortical desynchronization. Small doses of thiopental (i.e., 2 mg/kg) may likewise produce a similar pattern of electrocortical activation following the development of narcotic-induced delta wave activity.

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Title: RO 15-4513 antagonizes but not halothane anesthesia

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Introduction. Previous work has shown that RO 15-4513 and FG 7142, putative inverse agonists at the benzodiazepine receptor [1], reverse the behavioral and anticonvulsant effects of benzodiazepines, barbiturates, and alcohol [2,3,4]. FG 7142 km been shown to produce the opposite effects of a benzodiazepine agonist by being anxiogenic and at higher doses epileptogenic 5. It has been postulated that benzodiazepines and barbiturnes produce their sedative and hypnotic effects by binding to adjacent receptors in the same membrane protein ionophore complex. Current theories regarding the mechanism of action of general anesthetics such as halothane are based on a generalized membrane disordering effect rather than a receptor-mediated process. Therefore, if these inverse agonists are acting at the benzodiazepine protein ionophore complex specifically then they would no be expected to influence the activity of volatile anesthetic agents. The resent study was undertaken to examine the effects of RO 15-4513 and FG 7142 on the anesthetic properties of pentobarbital compered with halothane in the rat.

Methods. 46 male Wistar rats (200-360 g) were studied. 30 15-4513 [Roche] and FG 7142 [RBI] were dissolved (3 mg/ml) or conication in a carrier solution of 95% saline, 2.5% alcohol and 2.5% emulphor. Both drugs were administered intraperitoneall / in dose (3 mg/kg) previously shown to reverse the behavioral effects of CNS depressants [1-4]. Halothane was administered in air using in 0.8 L flow through a temperature- and flow-compensated fluotecTM vaporizer delivered to a snug-fitting nose cone. A ow-flow vacuum connected to the nose cone insured continuous resh gas flow. The righting reflex was assessed by placing the nimal on his back and measuring the time required to regain a felly pright posture. A righting reflex was considered absent if the nimal did not right themselves within 10 sec.

In the first experiment [EXP.1], animals were randomly ssigned to two groups. One group received an injection of the arrier solution (1 ml/kg, n= 10) and the other received 3C 5-4513 (n=10). The animals were then immediately anesthetized vith halothane using a vaporizer setting of 4% for 2 minutes ollowed by 2.5% for 8 minutes. The nose cone was ther nmediately removed, the animals were placed on their back, and ne righting reflex was measured. One week later, the same group f animals [EXP.2] were restudied. Animals that had received lacebo previously were pretreated with FG 7142 (n=10), while nose that had received RO 15-4513 received carrier solution n=10). Halothane was then administered beginning 5 minutes iter using the same protocol as in EXP.1 and righting reflex wis neasured. In experiment 3 [EXP.3], animals were randomized to eccive either RO 15-4513 (n=8) or carrier (1 ml/kg, n=8). ninutes later, halothane was administered, this time in a dose of % for 2 minutes and 2.5% for 13 minutes. Righting reflex VIS ien assessed. One week later [EXP.4], the same animals week erandomized to receive RO 15-4513 or carrier and then, five inutes later they were all given pentobarbital (20 mg/kg i.p., 50 1g/ml premixed solution) and the time to loss of righting as well as ie time to return of righting was recorded. In a final experiment EXP.5], a new group of animals were randomized to receive ther FG 7142 (n=5) or carrier (n=5) and then, 5 min later, given entobarbital (20 mg/kg) and the loss of righting reflex was sessed as before.

Differences between groups in the presence or absense of lcss righting reflex were analyzed using Chi-squared contingency ble analysis while differences in the time to onset and to recovery righting between groups were analyzed with one-way ANOVA. Il data were expressed as mean ± S.E.M.and a P value less then 5 was considered statistically significant.

Results. There were no differences between groups in mean animal weight in any experiment. The rerandomization between EXP.3 and EXP.4 was successful (P=0.61 by contingency table analysis). As can be seen from the table, neither RO 15-4513 nor FG 7142 had a significant effect on the recovery of righting reflex after halothane anesthesia. In EXP.4, while 7 out of 8 animals receiving placebo lost their righting reflex after pentobarbital (20 mg/kg), only 3 out of 8 of the RO 15-4513 (3 mg/kg) animals became anesthetized (P<0.05). In contrast, FG 7142 (3 mg/kg) had no influence on the response to pentobarbital.

Discussion. The ability of RO 15-4513 to reverse an anesthetic state produced by pentobarbital is consistent with previous work and supports the hypothesis that this compound is a benzodiazepine inverse agonist. In contrast, it is interesting that FG 7142 did not have an effect on pentobarbital anesthesia. This suggests that although both RO 15-4513 and FG 7142 have been identified as benzodiazepine inverse agonists with similar potencies, RO 15-4513 may have more of an (indirect or direct) effect on the barbiturate binding site associated with the receptor protein ionophore complex. Multiple doses must be studied to insure that this is not a dose-related difference in effect. The fact that neither drug antagonized the loss of righting produced by halothane is in harmony with a non-receptor mediated mechanism of action for the volatile anesthetics. The results of the present study suggest that RO 15-4513, or a similar compound, may be clinically useful in antagonizing barbiturate or benzodiazepine overdosage but can not be expected to have an effect on volatile anesthetic action. Further dose-response studies must be performed to characterize this interesting drug interaction.

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The technical assistance of Natalia Rioseco-Terry was greatly appreciated. RO 15-4513 and midazolam were generous gifts from Roche Laboratories

TARLE

Exper#	Anesthetic	Reversal	# Loss of Righting	Time to Loss of Righting (min)	Time to Recovery (min)
EXP.1	Halothane	RO 15-4513	10		2.03 ± 0.28
	(10 min)	Carrier	10		2.50 ± 0.41
EXP.2	Halothane	FG 7142	10		4.10 ± 0.92
	(15 min)	Carrier	10		4.01 ± 0.83
EXP.3	Halothane	RO 15-4513	8		2.66 ± 0.47
	(15 min)	Carrier	8		2.89 ± 0.41
EXP.4	Pentobarb	RO 15-4513	3	5.6 ± 0.3	41.0 ± 9.8
	(20 mg/kg)	Carrier	7*	5.0 ± 0.3	43.8 ± 8.6
EXP.5	Pentobarb [20 mg/kg)	FG 7142 Carrier	5 4	4.9 ± 0.3	39.6 ± 8.6
	(20 mg/kg)	Carrie	4	5.6 ± 0.6	39.0 ± 4.2

^{*} P<0.05 by Chi-squared contingency table analysis

Title: CARDIOVASCULAR ACTIONS AND MAC OF A NEW INHALATION ANESTHETIC, 1653, IN SWINE

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<u>Introduction</u>. I653 (difluoromethyl 1-fluoro 2,2,2-trifluoroethyl ether) is a new inhalation anesthetic identical to isoflurane except for the substitution of a fluorine for the chlorine atom. Its blood/gas partition coefficient, 0.42 (1), is substantially lower than that of isoflurane, and lower than that of nitrous oxide (2), resulting in very rapid emergence from anesthesia. Toxicological studies have not revealed any toxic properties (3), and I653 is stable in sodalime (4). These advantages suggested further evaluation. Accordingly, we compared the cardiovascular actions of I653 with those of equipotent concentrations of isoflurane and with the values in the resting conscious state in chronically instrumented swine.

Methods. The UCSF Committee on Animal Research approved this study. Determination of MAC: We anesthetized 5 young domestic swine (17.2+1.3Kg) approved this study. with 1653 in oxygen, via a mask. Succinylcholine, 2mg/kg was administered into a cannula inserted into an ear vein. The trachea was intubated and the aninal ventilated, 20ml/kg; frequency was adjusted to maintain normocarbia. No other drugs were administered. MAC was determined by a modification of standard methods (5). The painful stimulus was a clamp applied to a dew claw instead of the tail. Throughout the determination of MAC each animal's temperature, measured by a thermister in the esophagus, was maintained at 38.5+0.2°C, with a circulating heated water pad. Chronic Instrumentation: After determination of MAC, lumbar aortic (retroperitoneally) and thermodilution pulmonary arterial (percutaneously) cannulae were placed and tunnelled subcutaneously to the mid-dorsum of the back where they exited the skin into velcro pouches. Lumena of the cannulae were filled with heparin and flushed every other day. Determination of Cardiovascular Effects: Before and after surgery, animals were familiarized with the laboratory, laboratory personnel and a swine sling (6). Three to seven days following surgery, with the animals in good health, each pig was placed in the sling. Cardiovascular measurements were performed after at least 10 minutes of stability; most animals appeared to be asleep; all were resting calmly. Following measurements in the conscious state, animals were anesthetized with either I653 or isoflurane in oxygen, in random order. The alternate anesthetic was administered 4-7 days later. The trachea was intubated after administration of succinylcholine, 2mg/kg iv. No other drugs were given. Animals were mechanically ventilated with a tidal volume of 20ml/kg and ventilatory frequency adjusted to maintain normocarbia throughout the experiment. Pulmonary arterial temperature was maintained within 0.50° of its initial value (conscious state). Measurements were repeated in random order at approximately 1.0, 1.5, and 2.0 MAC. Data and computed values for the conscious state and each anesthetic level were compared using analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons.

Results. MAC for 1653 was 9.4+0.7%. 1653 and isoflurane caused similar dose-related decreases in mean aortic blood pressure (BPa), cardiac output

(Qt), stroke volume, and oxygen consumption (VO2) (fig 1); heart rate (HR) increased and systemic vascular resistance decreased but did not change with depth of anesthesia with either agent. Neither anesthetic altered blood lactate concentrations. No values for 1653 differed from those of isoflurane at equipotent concentrations.

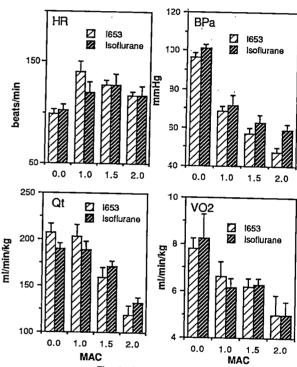


Fig 1: Data are mean +/- S.E.

Discussion. MAC for I653 is in keeping with the empiric relationship of anesthetic potency and solubility in olive oil (7). Although the solubilities of I653 and isoflurane in blood differ substantially, the cardiovascular properties do not. Given the similar chemical structures of the two anesthetics, it is not surprising that the cardiovascular actions of 1653 and isoflurane are similar. Our data indicate that 1653 has safe cardiovascular actions.

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1653, A NEW INHALATION ANESTHETIC, DOES NOT SENSITIZE SWINE MYOCARDIUM TO EXOGENOUS

EPINEPHRINE

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Introduction: I653 (difluoromethyl 1-fluoro 2,2,2-trifluoroemlyl ether) is a new inhalation anesthetic identical to isoflurane except for the substitution of a fluorine for the chlorine atom. Since inhalation anesthetics can affect the arrhythmogenic action of epinephrine, we compared the effect of exogenous epinephrine on cardiac rhythm in swine anesthetized with I653, isoflurane, or halothane.

Methods: This study was approved the University of California, San Francisco Committee on Animal Research. Anesthesia va: induced in four domestic swine (17.3 ± 1.5Kg) with eitLer halothane, 1653, or isoflurane, in random order, via a mask. Or separate days (at least 3 days apart) each animal received the order anesthetics. The trachea was intubated after succinylcholine, 2mg kg iv. No other drugs were administered. Ventilation was controlled: tidal volume was 20ml/kg; frequency was adjusted to maintain normocarbia. Epinephrine was infused intravenously after at least 15 min of stable end-tidal anesthetic concentrations of LO and 1.5 MAC, in random order. Epinephrine was infused ir increasing doses, for 5 min at each consecutive rate: 0.2, 0.4, 0.8 2.0, and 4.0 µg/kg/min. Infusion was stopped when the animal exhibited three premature ventricular contractions (PVC) withir one minute. If no PVCs occurred with 4.0,4g/kg/min, we did LCt infuse a greater rate; for purposes of analysis we treated the data at if the animal would have developed arrhythmias at the next higher rate (8µg/kg/min). Epinephrine infusion rates at which 3 PVCs in one min occurred were compared at equipotent concentration: Di the three anesthetics by analysis of variance and Newman-Ketls method of multiple comparisons. Statistical significance was accepted at P < 0.05.

Results: At both anesthetic concentrations (1.0 and 1.5 MAC) arrhythmias occurred with significantly lower infusion rates of epinephrine with halothane than with either I653 or isoflurane (Figure 1). There was no difference between the arrhythmogenic epinephrine infusion rate for I653 and for isoflurane at either 1.0 or 1.5 MAC. The arrhythmogenic dose of epinephrine did not vary with anesthetic concentration for any agent.

Discussion: Epinephrine more readily produced arrhythmias in the presence of halothane than isoflurane or I653. This relationship for halothane and isoflurane is well-known and the apparent similarity of the data for isoflurane and I653 suggests that the guidelines for the use of epinephrine in the presence of I653 will be similar to those presently applied to isoflurane. However, we have not adequately tested the difference between isoflurane and I653 because only one animal with I653 and two with isoflurane developed PVCs at the highest epinephrine infusion rate. The apparent absence of an arrhythmogenic effect of I653 suggests that I653 may be useful for surgery during when epinephrine is used, or when sympathomimetic drugs may be administered.

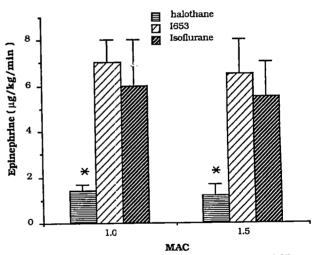


Figure 1. Data are mean ± S.E.

•=P<0.05

THE EFFECTS OF CHEMOSTIMULATION AND POSTURE ON POSTOPERATIVE

RESPIRATORY PATTERNS

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INTRODUCTION Pulmonary complications are the major cause of postoperative morbidity, with an incidence as high as 20-30% after upper abdominal surgery (UAS). Many studies have demonstrated significant decreases in static lung volumes (vital capacity, functional residual capacity) for over a week following such surgery. Associated with this is a breathing pattern characterized by an elevated respiratory rate, smaller tidal volume and an absence of sighs. A marked reduction in the ratio of abdominal to rib cage motion has been observed after UAS, reflecting severe diaphragmatic dysfunction (1). This study seeks to further the respiratory patterns cholecystectomy and specifically addresses the following:

A. It is recommended that after UAS, patients be nursed with the head of the bed elevated. Studies in normal subjects note an abdominal predominance in the supine position with an increase in rib cage motion when sitting (2). What is the difference in the postoperative setting (where there is a rib cage predominance) between the supine and sitting positions?

B. Chemostimulation with elevated inspired carbon dioxide concentration increases rib cage motion (3). After UAS, what happens when patients are so

chemost imulated?

METHODS Eleven otherwise healthy female patients (mean age 44 ± 17 (SD) years) undergoing elective cholecystectomy were studied on the afternoon prior to surgery and on the first and third postoperative days. Measurements of breathing patterns, oxygen consumption (VO2), and carbon dioxide production (VCO2) were made with a canopy-spirometer-computer system (4) coupled to a respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc.) for measurements of rib cage and abdominal motion. The canopy spirometer was used to calibrate the plethysmograph. Each study period consisted of measurements in the semi-erect (SE) position (head of bed at 30°) breathing room air (RA) followed by those in the supine (SU) posture breathing room air and then supine breathing 4% CO2. Ten minute recordings were made at each condition only once the VO2 and VCO2 were stable. On the first and third postoperative days, measurements were made at least 3 hours after an intramuscular dose of morphine. This study was approved by the Institutional Review Board.

RESULTS (mean ± S	SD)			·
RC/VT	V⊏	f.	٧ ٠	r.
PRE OP	SD) V _E I/min 4.51+0.87	(min-1)	(m1)	T (sec)
SE-RA 0.37±0.12 [†]		18±4	271±78	1.56±0.69
SU-RA 0.33±0.15	4.32±0.80	19±3	249±46	1.36±0.24
SU-CO ₂ 0.39±0.12 [†]	6.37±1.60	20±4	338±82	1.38±0.32
DAY I - POST OP			_	
SE-RA 0.53±0.17*	4.71±1.08 4.83±1.15* 7.29±2.20*	20±3 [*]	246±46	1.18+0.13*
SU-RA 0.54±0.23*	4.83±1.15°	21±4*	241±45	1.24±0.24
SU-CO ₂ 0.58±0.20*	7.29±2.20*	22±4*	333±85	1.16±0.17*
DAY 3 - POST OP		_		
SE-RA 0.44±0.11	4.76±1.12	19±3	253±57	1.21±0.21*
SU-RA 0.40±0.19	4.86±1.12*	20+3	247±53	1.18±0.18*
SU-CO ₂ 0.44±0.15 [†]	7.31±2.41*	21±4	348±93	1.19±0.19*
-			J .JI/J	1017 2017

RC/VT - proportion of VT contribution by rib cage VE - minute ventilation f - frequency

V_T – tidal volume T_I - inspiratory duration PRE OP DAY 1-POST OP DAY 3-POST OP VO2 VCO2 VO2 VCO2 VCO2 VCO2 SE-RA 168±30 146±25 180±19*147±17*186±28* 154±21* SU-RA 170±22 140±14 183±23 151±18 190±31* 159±19* * different than pre op value (p< 0.05) t different than supine value (p< 0.05)

DISCUSSION Cholecystectomy results in major changes in respiratory pattern. On the first postoperative day, there was an increase in minute ventilation especially in the SU position, due to a significant increase in frequency with little change in tidal valume. Also there was an increase in metabolic rate and a major shift to rib cage motion. By the third postoperative day RC/VT and respiratory rate started to return to pre-op levels. However, the VE and metabolic rate remain elevated. It thus appears that two mechanisms may be operative: The increased minute ventilation due to the increased metabolic demand and the change in rib cage:abdominal motion and breathing rate associated with stimulation and surgery of the upper abdomen. The latter abnormalities appear to resolve more rapidly than the increase in metabolic rate.

UAS altered postural effects. Preoperatively, RC/VT decreased when the patient was supine but on the first postoperative day the RC/VT was unchanged. Also comparing pre to postoperative values, VE increased in the SU but not SE position. The reason for this difference is unclear. Normally in the supine position the abdominal contents push the diaphragm into an ideal length tension relationship, facilitating a switch to efficient diaphragmatic breathing. Postoperatively, diaphragmatic function was markedly reduced thus likely abolishing the differences between supine and sitting patterns. This decreased diaphragmatic activity also effects the response to chemostimulation. There is an increase in the rib cage contribution pre-op but not on the first post-op day. In fact, pre-op 60% is contributed by the abdomen while postop 60% is contributed by the rib cage. It is possible that in the situation where there is already maximal use of the rib cage additional stimulation is unable to recruit these muscles further. Attempts at administering 6% CO2 were thus not tolerated on the first post-op day.

This study further demonstrates the inefficiency of supine postoperative respiration, thus reinforcing the practice of nursing such patients semi-erect. These observations also serve as a basis for future investigations of the effects of analgesia especially in view of the observations that rib

cage motion is reduced by narcotics (5).

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COMPARISON OF MIDAZOLAM AND DIAZEFAM AS ADJUVANTS TO KETAMINE FOR SEDATION DURING tle:

MONITORED ANESTHESIA CARE

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Introduction. A recent survey revealed that cal anesthesia with intravenous (iv) sedation was sociated with a higher complication rate than ther general or regional anesthesia (FASA, 1986). mbinations of benzodiazepines and narcotic analsics are frequently used to provide anxiolysis, dation, amnesia and analgesia during local anesesia. Unfortunately, these drug combinations can oduce significant respiratory depression. Use of tamine in combination with diazepam can produce dation and analgesia without depressing ventila-

on (Rust et al., 1978). We designed a two-part udy to compare the clinical efficacy and recovery aracteristics of midazolam (a newer benzodiazene) with diazepam when used in combination with tamine for iv sedation during local anesthesia. Methods. In an initial dose-ranging study, 120 althy, consenting outpatients undergoing plastic rgery with local anesthesia were studied accordig to a double-blind protocol approved by the stitutional Review Board. These unpremedicated itients we treatment groups (n=20/group). itients were sedated with diazepam (5 mg/ml) 0.1, 2 or 0.3 mg/kg, iv or midazolam (2.5 mg/ml) 0.05, 10 or 0.15 mg/kg, iv administered over 30-90 s. absequently, ketamine (0.5 mg/kg) was infused over 2-3 minute period immediately prior to the substanenous injection of local anesthetic solution. uring the operation, additional 0.5 ml doses of iazepam (2.5 mg) or midazolam (1.25 mg) were ljected as needed to maintain adequate sedation. ital signs were monitored using a Dinamap R and a $\!\!$ $\!\!$ $\!\!$ all $\!\!$ or $\!\!$ pulse oximeter. The degree of sedation as rated on a six-point scale by a blinded obser-1=awake/anxious, 2=awake/quiet, =awake/drowsy, 4=asleep/easily arousable, =asleep/difficult to arouse, and 6=asleep/unarousble (with 1-2=inadequate; 3-4=adequate; and 5=excessive sedation). The patient assessed their
nxiety, sedation, and pain on a four-point scale: nxiety, sedation, and pain on a four-point scale:
-none, 2=slight, and 3=moderate, and 4=marked. In
follow-up study, an additional 60 unpremedicated
utpatients were randomly assigned to receive
quivolumic doses of either diazepam, 0.2 mg/kg,
v, or midazolam, 0.1 mg/kg, iv, according to a
imilar double-blind protocol. The preoperative
valuation included sedation analog scales amposic valuation included sedation analog scales, amnesia est, Trieger psychomotor test, and mood assessment uestionnaire. These tests were repeated ostoperatively at hourly intervals until disharge. Analysis of variance was used to analyze ontinuous variables (mean values + S.E.M.), while lescriptive variables were analyzed using Chi-

quare tests, p < 0.05 was considered significant.

Results. With respect to demographic data, here were no significant differences among the six reatment groups. During the operation, no significant changes in blood pressure, heart rate, 'espiratory rate or oxygen saturation were noted. I majority of the patients in the diazepam groups were judged to be adequately sedated (55-80%), while the low-dose midazolam group were often undersedated (45%) and the high-dose group were frequently oversedated (75%). With respect to its sedative properties, midazolam was 2-4 times more

potent than diazepam (fig. 1). Anxiety scores were significantly lower following midazolam compared with diazepam in all dosage groups. The amnestic effects of both benzodiazepines were dose-related, with 30-70% of the patients failing to recall being discharged from the recovery room. In the followup study, midazolam was found to be significantly more potent than diazepam (maintenance dosage: 7.3+0.8 mg vs. 17.8+1.8 mg). Although the midazolam group had higher maintenance sedation scores, postoperative side effects and discharge times were similar for the two groups. Compared to the diazepam group, the midazolam group reported significantly less anxiety (1.2+0.1 vs. 1.6+0.1) and expressed greater satisfaction with their operative experience (81% vs. 49%). No unpleasant dreams were reported in either group. The incidence of pain on injection and postoperative venoirritation was significantly higher in the diazepam group (37% <u>vs</u>. 3%).

Discussion. A combination of either diazepam (0.2 mg/kg iv) or midazolam (0.1 mg/kg iv) with low-dose ketamine produced optimal sedation and analgesia without cardiovascular or respiratory depression. Midazolam would appear to offer an advantage over diazepam because its use was associated with less pain on injection and venoirritation, more profound intraoperative anxiolysis, sedation, and amnesia, and higher overall patient acceptance. However, the narrower therapeutic dosage range for midazolam (fig. 1) emphasizes the importance of careful titration to avoid excessive sedation. Finally, residual amnesia may be a problem when large doses of midazolam are administered to outpatients. Further studies using more sensitive recovery tests are needed to determine "street fitness" (or home readiness) following use of these drugs in the outpatient setting.

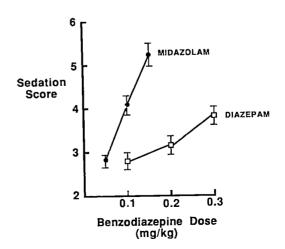


Figure 1: Dose-response curves for midazolam and diazepam following the initial dose (mean + SEM).

SHOCK PLUS AN INTRACRANIAL MASS IN DOGS: CEREBROVASCULAR EFFECTS OF RESUSCITATION FLUID CHOICES J.S. Whitley, Ph.D., D.S. Prough, M.D., D.S. DeWitt, Ph.D. Departments of Anesthesia and Neurology, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103 AFFILIATION:

Introduction: If intracranial hypertension occurs in combination with hemorrhagic shock, the choice of resuscitation fluids may strongly influence the extent of neurologic injury. dogs, the infusion of hypertonic saline (HSS) or hydroxyethylstarch (HSS) produces lower intracranial pressure (ICP) than resuscitation with isotonic crystalloid solutions (1,2). Although HSS reduces ICP to a greater extent than HES, the hemodynamic inprovement following HSS is more sustained than that following HSS. Recent studies of hemorrhagic shock have combined hypertonic and systemic hemodynamic improvement while preserving the advantages of a lower infusion volume (3). The cerebrovascular effects of such a combination nave not been reported. In anesthetized dogs with a subdural mass lesion, we induced hemorrhagic shock and compared the effects of resuscitation with a hypertonic, a hyperonoctic, an isotonic, or a combined hyperconic—hyperonoctic fluid on ICP and cere hard of the cerebrated of the cerebrated of the cerebrated with thiopental 20 mg/kg, paralyzed with vocuronium 0.2 mg/kg, and endotracheally intunted. We maintained anesthesia with nitrous oxide 60% and halothane 0.5% in oxygen eventileted to maintained anesthesia with nitrous oxide 60% and halothane 0.5% in oxygen and cerebrated with exercine magna, and two femoral arterial exherters were placed. CEF was measured using a sagittal sinus cannula. Through a left cranictomy, a subdural balloon was placed. While ICP was maintained at 20 mmHg by balloon inflation, at the saminal was rapidly hemorrhaged to reduce mean arterial pressure (MAP) to 50 mmHg where it was maintained for 30 min. Resuscitation fluids: 1. NGC 10.8% - 54 ml/kg (REC); 3. NGC 17.2% - 6.0 ml/kg (RES), 4. HES 20% in NGC 17.2% - 6.0 ml/kg (RES), 3. NGC 17.2% - 6.0 ml/kg (RESS), 4. HES 20% in NGC 17.2% - 6.0 ml/kg (RESS), 4. HES 20% in NGC 17.2% - 6.0 ml/kg (RESS), 4. HES 20% in NGC 17.2% - 6.0 ml/kg (RESS), 4.

produced only a transient improvement in systemic hemodynamics. If these data are extrapolated to human trauma victims in whom head injury is combined with hemorrhagic shock, a hyperoncotic/hypertonic or a hyperoncotic solution may be preferable for acute resuscitation.

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Figure I.

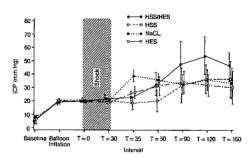
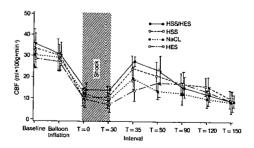


Figure II.



<u>litle:</u> INTRANASAL MIDAZOLAM PREMEDICATION IN PFE-SCHOOL CHILDREN.

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Introduction: Midazolam has been recommended as a preanesthetic medication in children, and it's administration via rectal (1) and intramuscular (2) route have been described. Administration via the nasal route has potential advantages over other routes, as rapid absorbtion with avoidance of "first pass metabolism" is possible and painful injections are avoided.

The objects of this study were to evaluate the efficacy of two doses of midazolam as a pre-operative sedative in pre-school children, and to specifically determine it's effect on separation from parents and on the response of the child to induction of anesthesia.

Methods: Following human use comittee approval and informed parental consent, 37 pediatric patients aged between 18 months and 5 years, presenting for anesthesia and surgery were randomly allocated to one of three groups and surgery were randomly and cards to one of these georges in a double blind manner. Group A (n=13) recieved normal saline (volume = 0.2ml/5kg), group B (n=12) recieved midazolam 0.2mg/kg (volume = 0.2ml/5kg) and group C (n=12) recieved midazolam 0.3mg/kg (volume = 0.3ml/5kg). All drugs were given intranasally to the child

in the presence of the parents.

The level of sedation was measured using a numerical scoring system as follows: (1) Agitated - clinging to parent and/or crying, (2) Alert - awake but not clinging to parent: may wimper but not cry, (3) Calm - sitting or lying with eyes open, (4) Drowsy - eyes closed but responds to minor stimulation, (5) Asleep - does not respond to minor stimulation. Oxygen saturation was measured continuosly during the study period using a Nellcor pulse oximeter, and heart rate and respiratory rate measured at intervals along with the sedation score. Following control measurments the drug was administered and measurements made every 2.5 minutes for 10 minutes. At 10 minutes following drug administration the child was separated from his/her parents and the response noted. At 15 minutes inhalational anesthesia was induced via appropriate mask and circuit. The response to induction was graded by modifying the sedation score as follows: (1) Agitated refuses mask and or cries, (2) Alert - may refuse mask initally, but accepts with persuasion: may wimper, (3) Calm - accepts mask, (4) Drowsy - accepts mask, (5) Sleeping.

Results: The mean age and weight of the children was similar in all groups. The level of sedation at 0, 7.5, 10, and 15 mins after drug administration is shown in table 1. Although the sedation score is arbitrarily catagorical, each level represents an approximately equal degree of change, therefore statistical analysis for continuous data was used. Two factorial repeated measures analysis of variance showed a significant interaction between the drug and repeated measures over time (p<0.03), therefore each factor was analyzed separately. The drug effect at each time period was analyzed by analysis of variance (ANOVA), and for each drug group the time effect was analyzed by onepopulation repeated measures analysis of variance.

At 7.5 mins patients in group B were more sedated than the other two groups, at separation (10 minutes) both drug groups (B&C) were more sedated than control group, and at induction (15 minutes) both drug groups (B&C) tolerated induction better than the control group (p<0.05). There was no difference between groups B and C

In the control group (A) some increasing sedation was seen with repeated measures at the time of separation for the parents (p<0.05). With both drug groups (B and C), increasing sedation was seen at 7.5, 10, and 15 minutes (p<0.01).

Heart rate, respiratory rate and oxygen saturation did not differ between groups and did not change significantly during the study period.

<u>Discussion</u>: The efficacy and safety of intra nasal midazolam as a rapidly acting pre-operative sedative in preschool children has been demonstrated. The importance of a control group was seen as group A showed increasing sedation with time until separation from parents, presumably because the child became used to the observer. This effect was not apparent at induction. In both groups receiving midazolam (B&C) the degree of sedation was more marked than group A when the children were separated from their parents and this level of sedation was maintained at induction.

Although not measured on the sedation score, it was noted that many of the patients receiving midazolam at either dose became mildly euphoric as their sedation score reached levels 3 and 4.

No dose response effect was seen, but it is not known whether this represents a "ceiling" therapeutic effect at the lower dose or whether maximal rapid intra nasal absorbtion occurred with the lower dose, and the extra volume used with the higher dose was then lost from the nose and swallowed.

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Table 1: Sedation level of patients during study period

SED. SCORE		0 min	DL .	7	'.5 mir	ו		IO min ARAT			5 min OUCTK	
SCORE	A	В	С	Α	В	С	A	В	C	Α	В	С
1	5	3	4	1	ŀ	-	1	-	-	7	-	-
2	7	6	6	5	-	1	6	2	-	0	2	3
3	1 1	3	2	7	7	11	6	4	9	6	4	6
4	ا . ا	۱.	-	۱.	5	- 1	-	6	3	-	6	3
5	-		-	-	-	Ŀ	-	Ŀ	-		Ŀ	<u> </u>

POTENCY OF MIVACURIUM CHLORIDE (BW B1090U) DURING HALOTHANE-NITROUS OXIDE AMESTHESIA IN CHILDREN Title:

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Introduction. Mivacurium (BW B1090U), a shortacting nondepolarizing neuromuscular blocker, is rapidly metabolized by human plasma cholinesterase. Therefore, it may be a clinically useful drug in situations where succinylcholine is undesirable. We determined the mivacurium dose-response relationship, onset time, and recovery indices in children during halothane-nitrous oxide anesthesia.

Methods. Thirty-five children (ASA status I-II) between 2 and 12 years old, having low-risk elective surgical procedures were studied. The study was approved by the Human Rights Committee of the Children's Hospital of Pittsburgh; informed consent was obtained from a parent. No patient received aminoglycoside antibiotics or antihistamines within 48 hours of the study. Premedication was not given. Anesthesia was induced with nitrous oxide (70%), oxygen (30%) and halothane (up to 4% inspired). After induction, an intravenous catheter was placed and atropine (10 µg/kg) was given. After endotracheal intubation, the end-tidal halothane concentration was adjusted to 0.8 \pm 0.05%; fentanyl (1-3 µg/kg) was given as needed.

The ulnar nerve was stimulated supramaximally with repeated trains-of-four stimuli (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan Bennett/ Datex monitor. The degree of neuromuscular blockade was described as percent of control, that is the height of the first train-of-four response was compared with the control EMG height. Blood was obtained for measurement of pseudocholinesterase activity and dibucaine number.

An initial dose of 20 µg/kg of mivacurium was given to three patients. This dose was selected as an estimate of ED25 based on previous data in adults and the expected degree of potentiation by halothane. The results were used to select further doses to estimate the dose response relationship. Subsequent patients received 40, 60 or 70 µg/kg of mivacurium. Each bolus of mivacurium was administered over less than five seconds through a T-connector into a rapidly running intravenous infusion. One patient was omitted from analysis because of abnormally high pseudocholinesterase activity. Each of 26 patients contributed one data point to the dose-response relationship. Doseresponse curves were determined by log-probit transformation of the data and calculation of least squares regression lines.

Another eight patients were anesthetized in a similar manner and received the ED95 dose of mivacurium. Two patients with abnormally high pseudocholinesterase activity were omitted from analysis. The onset time, maximum degree of neuromuscular blockade, and time for neuromuscular transmission to return to 25% (T25) and 75% (T75) of control after the bolus were noted. Blood pressure and heart rate were recorded at 1-min intervals for 5 minutes after the bolus. The recovery index (T25-T75) was calculated for all appropriate patients.

Standard deviations are shown for all mean values. Repeated measures analysis of variance was used to analyze cardiovascular data. Statistical differences were considered significant at $P \leq 0.05$.

Results. The ED25, 50, 75, and 95 during nitrous oxide-halothane (0.8% ET) anesthesia were 42, 57, 79, and 124 $\mu g/kg$, respectively (R = 0.69). The onset time to maximum block, duration of block, and recovery data following a single bolus of 120 μg/kg mivacurium are presented in Table 1. Four patients developed complete neuromuscular blockade after 120 ug/kg mivacurium: neuromuscular transmission recovered to 25% between 5.3 and 17.7 minutes after the initial bolus. No significant changes in heart rate or blood pressure occurred after rapid bolus administration of mivacurium. No skin flushing was observed.

Discussion. The dose-response relationship for mivacurium in these children is different from that previously reported by us in adults during isoflurane anesthesia (1), and suggests that children may be relatively resistant to mivacurium induced blockade. The current studies of mivacurium are incomplete in that the anesthetic backgrounds of the pediatric and adult dose-response studies are not strictly comparable, although previous studies of d-tubocurarine suggest that 0.5% isoflurane potentiates neuromuscular blockade to a similar degree to that of 0.8% halothane (2). Completion of dose-response studies under balanced anesthesia will clarify the age-related differences in response to mivacurium.

No signs of histamine release were observed in these children. Studies at higher dosages will further define the rapidity of onset, duration of clinically useful blockade and potential for side effects of mivacurium in pediatric patients.

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Table 1. Neuromuscular Data: Mivacurium 120 μg/kg in Children

	Max Block	Onset	T25-T75	
	%	to maz block min	min	
N =	5	5	6	
X + SD	99 <u>+</u> 0.4	2.1 <u>+</u> 0.5	4.2 <u>+</u> 1.9	
Range	99 - 100	1.7 - 3.0	3.0 - 8.1	

TITLE : NON-INVASIVE CARDIAC OUTPUT: TWO MEASURMENT METHODS COMPARED WITH THERMODILUTION AND THE

IMPORTANCE OF MEASURED HEART RATE AND EJECTION TIME

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INTRODUCTION. Thoracic bisimpedance and continuous wave Doppler ultrasonography are two non-invasive methods of measuring cardiac output (CO) that have been shown to correlate with cardiac output by thermodilution (COtd) (1,2).

Bioimpedance calculates stroke volume (SV) according

$$SV = \frac{L^3 * VETbi}{4.25} * \frac{dZ/dt max}{Zo}$$

where L = 0.17 * patient height (cm)
 VETbi = ventricular ejection time (sec)
 dZ/dtmax = maximum rate of impedance change

(ohm/sec)
Zo = baseline impedance (ohm)

Doppler ultrasonography calculates SV according to:

$$SV = CSA * VETdopp V$$

Although the radial artery is very distal to the aorta, the time from the onset of the systolic pressure up-stroke to the dicrotic notch (VET) has been reported to be the same in the carotid and racial arteries (3). Heart rate (HR) and VET are measured displayed and used by both non-invasive methods to calculate CO. Can VET estimated by radial arterial pressure tracing analysis (VETa) and HR by EKG (HRekg) be used to verify the accuracy of CO by doppler ultrasound (COdopp) or CO by thoracic bioimpedance (CObi)? The purpose of this study was to determine whether the correlation of VETa to VETbi or VETdopp affected the correlations of CObi and COdopp to COtd.

METHODS. This study was approved by the institutional review board. Critically ill patients requiring pulmonary artery catheters were eligible for study entry. COdopp was measured by a Lawrence 3000 (Paramus, NJ) with a suprasternal probe. Midway through the study, the doppler software was revisec so that COdopp was calculated after 6 beats (COdoppnew) instead of 12 beats (COdoppold). CObi was messured by a Bomed NCCOM 3 (Irvine, CA) monitor. COtd was measured with Edwards Swan-Ganz (Irvine, CA) catheters by injecting 10cc of D5W at room temperature. All devices were calibrated and used accorcing to manufacturer's recommendations. Simultaneous measurements of CObi, COdopp, COtd, VETbi, VETdopp, and VETa were obtained by two data collectors. $\ensuremath{\text{VETa}}$ was measured from a radial artery pressure trace. The NCCOM electrodes were applied first, then the suprasternal doppler probe was applied. When the doppler signal strength was optimized, one data collector injected the fluid for thermodilution measurement and recorded CObi and VETbi while the second data collector simultaneously recorded COdopp and VETdopp. COtd was recorded after calculation and display. HR by EKG (HRekg), bioimpedance (HRbi), and doppler (HRdopp) were recorded. COdopp and CObi were compared with COtd by correlation coefficient, regression analysis, bias and precision measurement.

RESULTS. Twenty-seven patients were studied. The statistical results are summarized in Table I. Neither method worked in one patient with atrial fibrillation and in another patient for unknown reasons. CObi but not COdopp was measurable in a patient with large chest excursions receiving positive pressure ventilation. COdopp but not CObi was measureable in a patient with pectus excavatum. HRbi and HRdopp were usually within 3 beats of HRekg. When they were not CObi and COdopp were inaccurate and were often not measurable. Selecting those CObi and COdopp where VETbi or VETdopp were within 40 msec of VETa improved the correlation coefficient of CObi, COdoppold, and COdoppnew with COtd. CObi correlated better with COtd than COdoppold. The correlation of CObi and COdoppnew to COtd was similar. The best correlation with COtd was with COdoppnew when VETdopp was within 40 msec of VETa. COdoppnew vs COtd also had the regression coefficients that most paralleled the line of identity.

DISCUSSION. CObi is measured continuously and once the electrodes are properly placed further CObi measurements do not depend on observer skill. COdopp requires technical skill for proper placement each time COdopp is measured. COdopp can be measured continuously with an esophageal probe but it currently is impractical in awake ICU patients. COdoppnew correlates better with COtd than COdoppold. Both devices would benefit from a real time display of doppler signal strength or bioimpedance and the ability to display trends in COdopp or CObi. HRekg and VETa may aid the interpretation of CObi and COdopp. REFERENCES.

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Table I: COtd vs COdopp and CObi

			•	•		
Group	1	11	111	1 V	٧	VI
n	115	49	53	17	183	89
r	.55	.66	.73	.82	.75	.76
x	.56	.38	.88	1.12	.51	-53
Ь	2.66	3.33	.31	-1.92	3.0	2.7
bias	.11	1.0	-59	.94	.23	.73
precision	1.89	1.96	1.88	1.99	1.40	1.71

group I = COtd vs COdoppold (12 beat software)
group II = COtd vs COdoppold [VETa-VETdopp] < 40msec
group III = COtd vs COdoppnew (6 beat software)
group IV = COtd vs COdoppnew, [VETa-VETdopp] < 40msec
group V = COtd vs CObi, all data
group VI = COtd vs CObi, [VETa-VETbi] < 40msec</pre>

T

n = number of data sets, r = correlation coefficient, x = regression coefficient, b = y intercept, COtd assumed to be the independent variable x in all groups.

Title: CEREBRAL PERFUSION DURING ARTERIOVENOUS MALFORMATION RESECTION

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Introduction. Hyperemia and subsequent hemorrhage in relatively normal brain is a major source of post-operative morbidity and mortality following resection of arteriovenous malformations After resection, flow from the AVM vascular bed is routed into tissue that is unable to effectively autoregulate and hyperemia or intraparenchymal hemorrhage may occur. We report our initial experience using intraoperative regional cerebral blood flow (rCBF) monitoring during 6 AVM resections, after which 2 patients developed complications felt to be related to perfusion pressure breakthrough (1).

Methods. After institutional approval, informed consent was obtained from 6 patients scheduled to undergo elective AVM resection. Anesthesia was induced with thiopental (4 mg/kg) and tracheal intubation facilitated with a nondepolarizing muscle relaxant. Patients received isoflurane (ISO) during induction and were maintained on 0.75 - 1.25% ISO in 6:4 nitrous oxide/oxygen. Monitoring included ETCO₂, radial arterial catheter, and rCBF device (Novo 10a^(R)). Determination of rCBF was by the iv 133 ke method using the Initial Slope Index. Data were collected from a detector positioned within 5-6 cm from the border of the AVM site within the main distribution of the primary arterial feeding supply. After exposure of the dura, an initial rCBF measurement (PRE) was done. To assess ${\rm CO}_2$ reactivity (COR), the p ${\rm CO}_2$ was then elevated 8-10 mmHg and another rCBF measurement was performed (PRE COR). The pCO₂ was then adjusted back to baseline levels for surgical dissection. After resection of the AVM was completed, rCBF was again measured (POST). To assess COR after AVM resection, in 2 patients a POST COR measurement Four patients (Group 1, NORMO) had was done. post-operative courses without development of hyperperfusion syndromes and 2 patients (Group 2, HYPER) developed complications attributable to hyperperfusion.

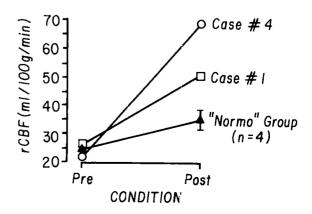
Results. There were 2 males and 4 females, 34-52 yrs old, who underwent surgery for moderate to large cortical AVMs. PRE rCBF and other physiological data (n=6, mean \pm SE) were similar for all patients: rCBF 24 \pm 2 ml/lOOg/min, Mean Blood Pressure 70 \pm 3 mmHg, and pCO₂ 27 \pm 2 mmHg. All cases were uneventful intraoperatively and no patient emerged from anesthesia with major neurological deficits. neurological deficits. There were two adverse outcomes attributable to hyperperfusion. Patient #1, who underwent a right temporal-occipital AVM resection, developed confusion and lethargy over the course of several days postoperatively and had significant brain swelling and midline shift in the ipsilateral frontal region on CT scan, corresponding to the area under the intraoperative rCBF detector. He fully recovered by 8 days postoperatively. Patient #4 underwent removal of a large temporal AVM. She did well until 6 h post-operatively she experienced when intracerebral hemorrhage (ICH) and was immediately re-explored and an artery near the AVM resection site was felt to be the source of bleeding.

However, 6 hours later she experienced a second ICH and was again re-explored. At the second operation, an artery well-removed from the operative site was found to be ruptured. patient never regained brain stem function and expired. Neither patient experiencing compli-cations had post-operative hypertension. The rCBF changes from PRE to POST for the 2 HYPER patients are compared to the mean of the NORMO (n=4) group in the Figure. In the NORMO group, rCBF significantly (p <0.02, Student's t-test) changed from 24 + 2 to 35 + 3 ml/lOOg/min from PRE to POST. Both patients in the HYPER group had large (>100%) elevations in rCBF after AVM resection. PRE COR was similar in both NORMO and HYPER patients and was 4.5 - 0.5%/mmHg. POST COR was available for patient #1 (8.5%/mmHg) and one patient from the NORMO group (4.5%/mmHg).

Discussion. Although it appears that obliteration of the shunt flow through the AVM raises rCBF even in patients not experiencing post-operative complications attributable to hyperperfusion, patients that have very large (>100%) increases in rCBF after AVM resection may be at an increased risk for post-operative complications. PRE COR was preserved in both patients that went on to suffer hyperperfusion complications. Furthermore, in at least one of the HYPER patients, POST COR was preserved or enhanced. The presence of maintained COR calls into question some aspects of the previously proposed mechanism of normal perfusion pressure breakthrough (1). In conclusion: 1) Intraoperative rCBF measurements may be of use in identifying patients at risk for developing postoperative hyperperfusion and subsequent complications; 2) Since both complications occurred even in the absence of hypertension, it may be of critical importance to very strictly control emergence and post-operative blood pressure after removal of an AVM to prevent hyperperfusion complications.

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ANESTH ANALG 1988:67:S1-S266

Title: DOES TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION PROVIDE PAIN RELIEF AFTER LUMBAR LAMINECTOMY?

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Introduction: Several investigators have reported that transcutaneous electric nerve stimulation (TENS) in the postoperative period decreases pain (1), reduces the need for narcotics and improves ventilatory function (2). However in most of these studies the anesthetic given was not standardized and/or there was no "blinde-1" control group. Here we report the results of a double blind, prospective study to evaluate TENS for pain management after lumbar laminectorry with a standardized anesthetic and a sham treatment group.

After Institutional Review Board approval thirty Methods: consenting patients undergoing primary surgery for a herniated nucleus pulposis of the lumbar spine were studied. Patients with prior TENS experience were excluded. Subjects were told that they might be in a sham group, that they might feel stimulation or nothing, but that the absence of sensation would not mean that the unit was not working. Patients were assured that they would have the same narcotics available regardless of the treatment group. All patients recieved $\ensuremath{\mathsf{M}}$ morphine/scopalamine for premedication and general endotracheal anesthesia with N20/02/meperidine/diazepam/pentothal/relaxant Subjects were randomly assigned to a SHAM or treatment (TEN3. group. After skin closure sterile electrodes were placed 2.5 cm. o either side of the incision and covered by the dressing. For the SHAM group a wire was cut and the ends concealed within the electrode. A Codman EPC@/Dual stimulator was used with a frequency of 80 Hz, pulse width of 170 μsec and an output that was subthreshold (usual γ between 20-30 ma). SHAM patients had comparable settings. The units were activated in the recovery room by a nurse just prior to patient discharge and ran continuously for 48 hrs. Batteries were changed at 24 hrs when the unit was also inspected. The nursing and surgical staff did not know the assigned treatment. Subjects were seen at 24 and 48 hrs by an anesthesiologist who was blinded to the treatment and he asked them to rate their pain on a 5 point (Melzacz) scale (0= no pain, 1=mild, 2=discomforting, 3-distressing, 4=horribb, 5=excruciating). They were also asked a series of yes-no questions about incisional pain, whether the TENS unit and/or narcotics helped pain, or whether the unit caused discomfort. Forced vital capacity (FVC) and forced expiratory volume (FEV1) were obtained at the bedside preoperatively, and at 24 and 48 hrs. Total patient narcotic usage was recorded as premedication + intraoperative + recovery room = ANES; 1st day = P01; 2nd day = P02. No attempt was made to change current postoperative analgesic practices and narcotics were given on demand as customary to the neurosurgical ward.

The hypotheses to be tested were that TENS: 1 - decreases the intensity of pain; 2 - decreases the dose of postoperative narcotics; and 3 -improves pulmonary function. Patient characteristics (age, weight, surgical time) and narcotic use were compared using a Student's t-test; yes-no questions were analyzed using the Chi squared test. The dose of narcotic used was calculated by multiplying the dose of a particular drug by its potency relative to meperidine. All narcotics were converted to IM Meperidine (Md) equivalents v a the ratios IM Md: IV Md: po Md: IM Morphine:po oxycodone=75:75:225:10:30 mg and the totals expressed in mg/kg (3).

Results. One patient in the TENS group and two in the SHAM group would not participate in the postoperative respiratory function tests or pain scale evaluations. Narcotic data is available for all patients. Patients in both groups had a similar age $(52 \pm 4 \text{ vs. } 45 \pm 3 \text{ yrs.})$, weight $(82 \pm 4 \text{ vs. } 83 \pm 4 \text{ kg})$ and length of surgery $(2.1 \pm .13 \text{ vs. } 13 \pm .17 \text{ hrs.})$. There was no difference in narcotic usage for the anesthet c (ANES) or for the postoperative periods in either group (Table I). FVC and FEV were significantly decreased from preoperative values in both groups; but there was no difference between the groups by Student's intest (Fig. 1).

6 of 14 responding TENS patients and 6 of 13 responding SHAM patients felt that TENS provided some pain relief during PO1 (7/14-TENS and 7/13-SHAM during PO2). 11/14 TENS and 12/12 SHAM patients felt that narcotics provided pain relief. During PO1 11/14 TENS patients rated pain as 0-2 (none, mild, discomforting) and only 3/14 as 3 (distressing), while 11/13 SHAM patients rated pain as 0-2 and 2/13 rated their pain as 4 (horrible). Statistical analysis showed no difference in all of the above by CHI squared tests.

Due to the lack of difference between groups we were concerned that our sample might not represent the population of patients undergoing lumbar spine surgery in our hospital; or that a possible bias occured from the study. Hence a historic control sample was obtained on age and sex matched patients having lumbar disc surgery the year prior to our study. Length of surgery (1.8 \pm .19 h) and weight was similar (82 \pm 6 kg) as was narcotic use (ANES= 2.33 \pm 0.22 mg/kg; PO1=3.44 \pm 0.83 mg/kg and PO2=2.25 \pm 1.06mg/kg).

<u>Discussion</u>. In contrast to other studies, our data showed no effect from TENS in the postoperative period. The dose of narcotic was equal in both groups, as was postoperative pulmonary function and the qualitative estimation of pain. We used a standardized anesthetic (as evidenced by similar narcotic doses) and a double blind design with a sham group which could account for our differences compared to other studies. The similarity of our historic control group does not support any pertubation in patient care due to the study. Our study does not support the use of TENS for pain control after lumbar laminectomy.

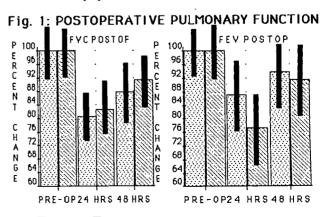
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TABLE I: NARCOTIC USAGE

TIME:	TENS	SHAM
ANES	2.69 ± 0.22	2.74 ± 0.16
PO 1	2.47 ± 0.44	2.92 ± 0.64
P0 2	2.06 ± 0.46	2.06 ± 0.31

All numbers in mg/kg of IM meperidne equivalents (see text).



☑TENS ☑SHAM ☑TENS ☑SHAM Values represent percent change from preoperative FVC and FEV (mean ± SEM).

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INFLUENCE OF NARCOTICS ON RECOVERY ROOM STAY AND ANALGESIC REQUIREMENTS

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Introduction technique is a combination of volatile anesthetic agents and narcotics. Proponents of pure inhalation anesthesia argue that intraoperative administration of a narcotic does not decrease postoperative analgesic requirements and prolongs recovery room stay (RRS). A one year prospective study of inpatients who received a volatile anesthetic and did not require admission to an ICU was conducted to evaluate the beneficial and detrimental effects of pre- and intraoperative narcotic administration.

Methods. Of the 2706 patients, 1323 male and 1363 female, 392 were children (12 years). Surgical procedures were categorized as: intraoral (IR), intracranial (IC), thoracic (IT), spine (SP), intraperitoneal (IP), abdominal, extraperitoneal (EP), laparoscopy (LP) and superficial (SF) (Table 1). Pre- and intraoperative administration of morphine (M), meperidine (D), and fentanyl (F) was documented (Table 2). Patients in Groups I, III and V received enflurane (E), isoflurane (I), or halothane (H) and no narcotic (O). Groups II, IV and VI received a narcotic (N) intraoperatively in addition to the volatile agent. Groups VII and VIII did not receive a volatile anesthetic agent: data from these 119 patients (4.7%), a heterogenous group receiving a variety of agents, were omitted from analysis (Table 3). All patients also received nitrous oxide. Patients were evaluated upon arrival in the Recovery Room (RR) and at 15 min. intervals using the Aldrete Scale (AS). The interval between termination of anesthesia and the first analgesic administration (AA) was documented. The five percent of patients in whom this interval exceeded 12 hrs were excluded from analysis because it was assumed that the N effects were no longer a major factor at that time and the interval was extremely variable (up to 44 hrs.). Student's t-test for unpaired samples and chi-square test were applied where appropriate.

Results. Narcotics were administered preoperatively (pre) to 289 patients (11.2%). Of 853 patients who received intraoperative N (intra), 802 (94%) received fentanyl (F). The median dose of F was 300 ug; 10% received 100 ug; 80% received 500 ug. The duration of anesthesia ranged from .25 h to 12.5 h (median 2.2 h). The mean AS on arrival in the RR was 6.8 regardless of whether pre or intra N were administered. The mean RRS was 58 min in patients who did and did not received pre N. However, RRS was 67 min with intra N and 54 without (p.01). The mean interval between the end

of anesthesia and AA was 3.1 h with pre N and 2.8 h without. With intra N it was 3.0 h and 2.7 h without (p .01).

Discussion. It is concluded that neither pre nor intraoperative narcotic administration influences the initial Aldrete Scores. Intraoperative, but not preoperative narcotic administration is associated with longer recovery room stay and longer interval between termination of anesthesia and postoperative analgesic administration.

Reference:

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Table 1		
Site	N	%
Superficial (SF)	1691	65.4
Intraperitoneal (IP)	525	20.3
Spine (SP)	110	4.3
Abd-extraperitoneal (EP)	81	3.1
Intraoral (IR)	76	2.9
Intracranial (IC)	56	2.2
Abd-laparoscopy (LP)	24	0.9
Chest (IT)	24	0.9

		Tal	ble 2			
Narcotic		M		D	F	
Pre-op Intra-op	N 224 45	% (77.5) (5.3)	N 65 2	% (22.5) (0.2)	N 802	(%) - (94.5)

	Table 3	
Anesthetic	N	%
I EO	1015	39.2
II EN	593	23.0
III IO	190	7.3
IV IN	167	6.5
V HO	529	20.4
VI HN	93	3.5

	Т	able 4	
Group	AS	RRS (m)	AA (h)
I	8.8	53.6	2.5
II	6.8	66.8	2.9
III	6.5	62.6	2.3
IV	6.5	68.6	3.2
V	6.7	51.4	3.4
VI	6.6	63.5	3.6

Title: THE ELECTROENCEPHALOGRAPHIC EFFECIS OF LAUDANOSINE IN A RABBIT MODEL OF EPILEPSY

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Introduction: Laudanosine, a known metabolite of the muscle relaxant atracurium, has been shown to be cause seizures in a variety of species.(1,2) The required plasma levels are much higher than those that would be expected following clinical use of atracurium. However, in the presence of cerebral patholog (brain tumor, trauma, seizure focus), it has been suggested that clinically relevant levels could provoke seizure activity. We therefore examined the EEG effects of laudanosine in an animal model of epilepsy.

Methods: 8 New Zealand white rabbits weighing 3.1 - 3.9 kg were anesthetized with 4% halothane in oxygen, paralyzed with pancuronium, intubated, and mechanically ventilated with 30%. O2 in nitrogen and 1.0% halothane. The PaCO2 was maintained between 35-45 mmHg. Esophageal temperature was monitored and maintained at 37° C through the use of servo-controlled heat lamps. A femoral arterial catheter was inserted for the continuous monitoring of arterial pressure. infiltration with 0.25% bupivacaine, the scalp was incised in the midline and reflected laterally to expose the skull. Brass screw electrodes were placed in the skull for the recording of the EEG. Biparietal craniotomies were made for the late application of gelfoam sponges soaked in a 4% cefazolin solution to the cortical surface. Control EEG recordings (C1) were made following completion of the surgical preparation. The animals were then randomly assigned to receive an infusion of eithelaudanosine (96 $\mu g/kg/min$) or saline for 10 minutes. The EEG was again recorded (C2) and the 4% cefazolin applied to the cortical surface. Infusions of laudanosine (24 µg/kg/min or saline were continued for the remainder of the experiment. Repeat recordings of the EEG were made at 5, 10, 20, 30, 45 and 60 minutes following the application of the cefazolin. These were subsequently scored in a blinded fashion for the frequency of spike and burst activity. All data were analyzed using unpaired t-tests. Significance was assumed for a p value of c 0.05.

Results: There were no significant differences between the two groups in terms of arterial blood pressure or blood gases during the experiment. As anticipated, analysis of the EEGs revealed a sharp increase in the frequency of spike and burst activity following the application of the 4% cefazolin solution There were no differences, however, between the saline anc laudanosine treated groups (Fig. 1 and 2). No sustained seizure activity was seen in any of the animals.

Discussion: Laudanosine is known to cause convulsions in animals at levels which greatly exceed those found in patients receiving atracurium. The possibility that clinically relevantevels may provoke seizures in patients with underlying cerebral pathology has been suggested.(3) In this animal mode of an epileptogenic focus, no increased incidence of seizure activity could be detected in those animals receiving laudanosine at rates sufficient to produce plasma levels of the drug similar to what might be seen following the clinical use of atracurium. (3)

SALINE SPIKE/BURST FREQUENCY

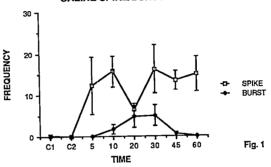


Fig. 1 Frequency (episodes/min ± SEM) of spike and burst activity in the EEG of control animals during the course of the experiment.

LAUDANOSINE SPIKE/BURST FREQUENCY

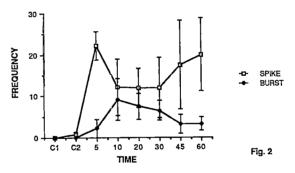


Fig. 2 Frequency (episodes/min \pm SEM) of spike and burst activity in the EEG of animals receiving laudanosine. (C1 = end surgical prep., C2 = following loading dose of laudanosine, immediately prior to application of cefazolin)

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TRACRIUM® INJECTION

(atracurium besvlate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular dis-ease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infants should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium suitate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been

ADVERSE REACTIONS

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%

Most adverse reactions were of little clinical significance unless they were associated with significant most adverse reactions were of intile clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of ouserved in Clinical Practice: based on Clinical experience in the 0.5. and the United Kingdom of approximately 3 million patients given Tractium the following adverse reactions are among the most frequently reported: General: allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest): Musculoskeletal: inadequate, prolonged block; Cardiovascular. hypotension, vasodilatation (flushing); tachycardia, bradycardia; Respiratory: dyspnea, bronchospasm, laryngospasm; Integumentary: rash, urticaria, injection site reaction.

¹Miller R. Rupp S, Fisher D, et al: Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984;61:444–453.

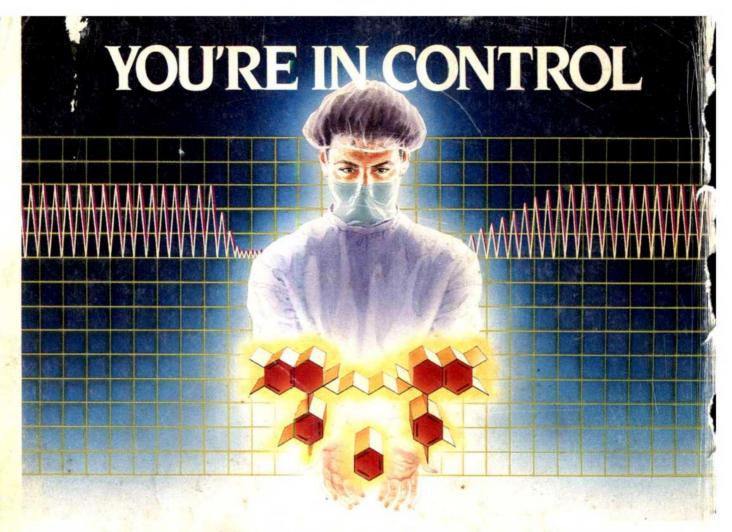
²Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p. 98.

³Eagar B, Flynn P, Hughes R: Infusion of atracurium for long surgical procedures. *Br J Anaesth* 1984;56:447–452.

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TRACRIUM® (atracurium besylate)
Injection is meaningfully different from all other neuromuscular blockers. TRACRIUM is inactivated in plasma by two pathways, Hofmann elimination and ester hydrolysis, that act independently of liver or kidney function. This unique metabolism can result in *superior control* and makes possible:

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Repeated equipotent doses of TRACRIUM, administered at equal intervals, have no cumulative effect.²

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(atracurium besylate)

